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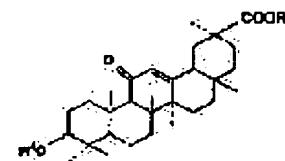
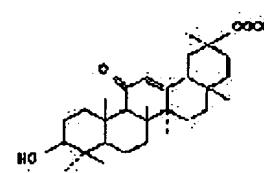
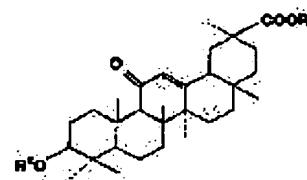
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(54) NOVEL GLYCYRRHETIC ACID-RELATED COMPOUNDS OF THEIR SALTS

(57)Abstract:

PURPOSE: To provide the subject novel compound having an excellent inhibiting effect against HIV infection, low in toxicity, high in safety, and useful as a virus infection-inhibiting agent for human acquired immunodeficiency syndromes.

CONSTITUTION: A glycyrrhetic acid-related compound of formula I [R1 is 1-18C alkyl; R2 is a group produced by combining one-seven SO₃M groups (M is H, alkali metal, alkaline earth metal atom) with the hydroxyl groups of a hydroxyl group-removed lactose residue]. For example, methyl-3-O-[2,3,4,6-tetra(sodium-sulfonato)- β -D-galactopyranosyl (1 \rightarrow 4)-2,3,6-tri(sodiumsulfonato)- β -D-glucopyranosyl]glyrrhetinate. The compound of formula I is obtained e.g. by reacting glycyrrhetic acid of formula II as a starting raw material with a specific alcohol, a saccharide compound and furthermore an inorganic or organic base, and subsequently combining the all hydroxyl groups of the produced compound of formula III [R4 is the residue of a disaccharide (lactose)] with SO₃M groups at an adjusted pH.



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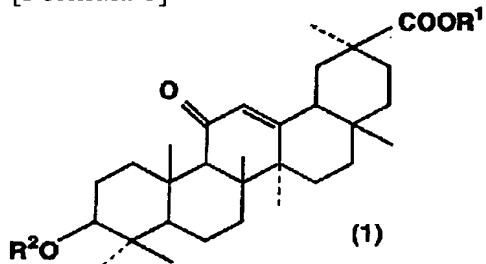
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CLAIMS

[Claim(s)]

[Claim 1] General formula (1)

[Formula 1]



They are the glycyrrhetic acid related compounds expressed with [what 1-7 SO3 M (M is a hydrogen atom or alkali metal, and an alkaline earth metal atom) has combined is shown in the hydroxyl group of the residue the inside R1 of a formula was excluding the alkyl group of carbon numbers 1-18, and excluding [R2] the hydroxyl group from the lactose], or those salts that are permitted in pharmacology.

[Claim 2] The Homo sapiens acquired-immune-deficiency-syndrome viral infection inhibitor which makes an active principle the glycyrrhetic acid related compounds shown in claim 1, or those salts that are permitted in pharmacology.

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DETAILED DESCRIPTION

[Detailed Description of the Invention]

[0001]

[Industrial Application] This invention relates to the Homo sapiens acquired-immune-deficiency-syndrome viral infection inhibitor which makes a glycyrrhetic acid related compound an active principle.

[0002]

[Description of the Prior Art] It is solved that acquired immune deficiency syndrome (henceforth an acquired immunodeficiency syndrome) is a disease by the virus [it is called an AIDS virus (HIV) below], and anti-AIDS virus agents, such as current azidothymidine and dideoxycytidine, are used. On the other hand, it is shown that glycyrrhizin controls growth of HIV by , and 4 times as strong ["Masahiko Ito et al., medical Ayumi, 141 427(1987)], and also a glycyrrhizin sulfation object] activity as glycyrrhizin is reported. in vitro [Nakashima et al., Jpn, J, Cancer Res., 78 767 (1987).]

[0003]

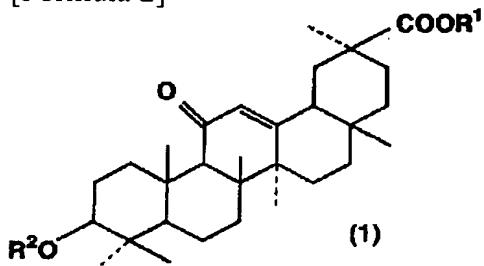
[Problem(s) to be Solved by the Invention] However, the anti-AIDS virus agent used now has high toxicity, and drugs with new high safety are desired.

[0004]

[Means for Solving the Problem] Then, artificers have the anti-AIDS virus operation with the sulfation objects and those salts of a new glycyrrhetic acid related compound more powerful one 10 to 100 times the number of this than the glycyrrhizin known conventionally and its sulfation object sodium salt as a result of examining many things, and it found out that it could be used as an anti-AIDS virus agent. That is, this invention is a general formula (1).

[0005]

[Formula 2]



[0006] It is related with the glycyrrhetic acid related compounds expressed with [what 1-7 SO₃ M (M is a hydrogen atom or alkali metal, and an alkaline earth metal atom) has combined is shown in the hydroxyl group of the residue the inside R1 of a formula was excluding the alkyl group of carbon numbers 1-18, and excluding [R2] the hydroxyl group from the lactose], or those salts that are permitted in pharmacology.

[0007] R1 in the general formula (1) in this invention if this invention is further explained to a detail The alkyl group of the straight chain of carbon numbers 1-18 is expressed, for example, a methyl group, an ethyl group, a propyl group, butyl, a pentyl radical, a hexyl group, a heptyl radical, an octyl radical, a nonyl radical, a decyl group, an undecyl radical, the dodecyl, a tetradecyl radical, a hexadecyl radical, an octadecyl radical, etc. are shown. R1 It carries out and a methyl group, an ethyl group, a propyl group, butyl, a pentyl radical, a hexyl group, a heptyl radical, an octyl radical, a nonyl radical, a decyl group, an undecyl radical, the dodecyl, etc. are mentioned preferably.

[0008] R2 ***** -- what 1-7 SO₃ M (M is alkaline-earth-metal atoms, such as alkali-metal atoms, such as a hydrogen atom or a lithium, sodium, and a potassium, or magnesium, and calcium) has combined with the

hydroxyl group of the residue excluding the hydroxyl group from the lactose, and has optical activity also contains an optical isomer.

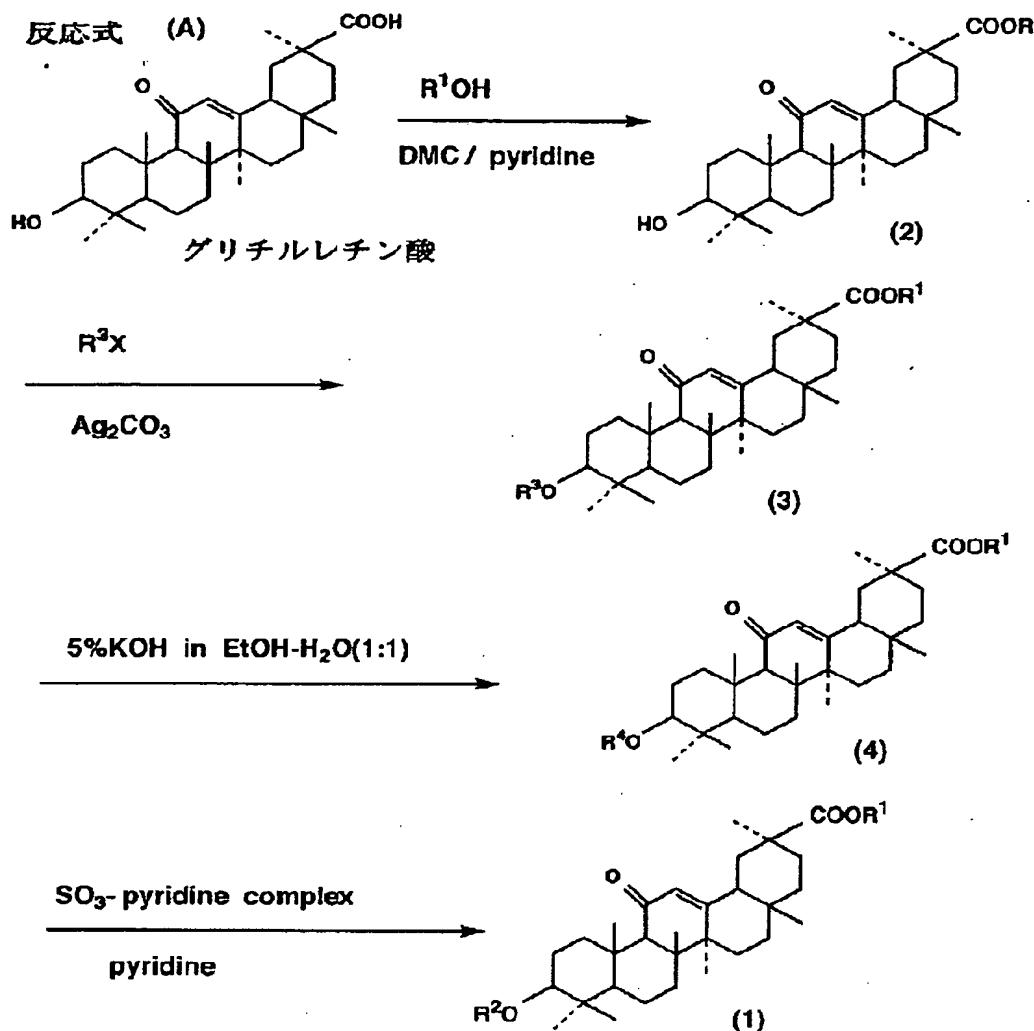
[0009] R2 It carries out and is specifically 2, 3, 4, and 6-tetrapod (sodium sulfonate)-beta-D-galactopyranosyl (1->4). - It is sodium salt of the disaccharide which the sulfuric-acid radical combined with the 2, 3, and 6-Tori (sodium sulfonate)-beta-D-glucopyranosyl radical etc.

[0010] The substituent R1 of a general formula (1), and R2 Although it carries out and a desirable thing is mentioned above As a compound of a desirable general formula (1) especially ** (1) methyl 3-O-{2, 3 and 4, and 6-tetrapod (sodium sulfonate)-beta-D-galactopyranosyl (1->4) - 2, 3, and 6-Tori (sodium sulfonate)-beta-D-glucopyranosyl} GURICHIRURETINATO (2) ethyl 3-O-{2, 3 and 4, 6-tetrapod () [sodium] sulfonate-beta-D-galactopyranosyl (1->4)-GURICHIRURETINATO [2, 3, and 6-Tori (sodium sulfonate)-beta-D-glucopyranosyl }] (3) propyl 3-O-{2, 3 and 4, 6-tetrapod () [sodium] sulfonate-beta-D-galactopyranosyl (1->4)-GURICHIRURETINATO [2, 3, and 6-Tori (sodium sulfonate)-beta-D-glucopyranosyl }] (4) butyl 3-O-{2, 3 and 4, 6-tetrapod () [sodium] sulfonate-beta-D-galactopyranosyl (1->4) - 2, 3, 6-Tori (sodium sulfonate)-beta-D-glucopyranosyl} GURICHIRURETINATO [0011] (5) pentyl 3-O-{2, 3 and 4, and 6-tetrapod (sodium sulfonate)-beta-D-galactopyranosyl (1->4) - 2, 3, and 6-Tori (sodium sulfonate)-beta-D-glucopyranosyl} GURICHIRURETINATO (6) hexyl 3-O-{2, 3 and 4, 6-tetrapod () [sodium] sulfonate-beta-D-galactopyranosyl (1->4)-GURICHIRURETINATO [2, 3, and 6-Tori (sodium sulfonate)-beta-D-glucopyranosyl }] (7) heptyl 3-O-{2, 3 and 4, 6-tetrapod () [sodium] sulfonate-beta-D-galactopyranosyl (1->4)-GURICHIRURETINATO [2, 3, and 6-Tori (sodium sulfonate)-beta-D-glucopyranosyl }] (8) octyl 3-O-{2, 3 and 4, 6-tetrapod () [sodium] sulfonate-beta-D-galactopyranosyl (1->4) - 2, 3, 6-Tori (sodium sulfonate)-beta-D-glucopyranosyl} GURICHIRURETINATO [0012] (9) nonyl 3-O-{2, 3 and 4, and 6-tetrapod (sodium sulfonate)-beta-D-galactopyranosyl (1->4) - 2, 3, and 6-Tori (sodium sulfonate)-beta-D-glucopyranosyl} GURICHIRURETINATO (10) DESHIRU 3-O-{2, 3 and 4, 6-tetrapod () [sodium] sulfonate-beta-D-galactopyranosyl (1->4)-GURICHIRURETINATO [2, 3, and 6-Tori (sodium sulfonate)-beta-D-glucopyranosyl }] (11) undecyl 3-O-{2, 3 and 4, 6-tetrapod () [sodium] sulfonate-beta-D-galactopyranosyl (1->4)-GURICHIRURETINATO [2, 3, and 6-Tori (sodium sulfonate)-beta-D-glucopyranosyl }] (12) dodecyl 3-O-{2, 3 and 4, 6-tetrapod () [sodium] sulfonate-beta-D-galactopyranosyl (1->4)-GURICHIRURETINATO [2, 3, and 6-Tori (sodium sulfonate)-beta-D-glucopyranosyl }] (13) octadecyl 3-O-{2, 3 and 4, 6-tetrapod () [sodium] sulfonate-beta-D-galactopyranosyl (1->4) - It is 2, 3, and 6-Tori (sodium sulfonate)-beta-D-glucopyranosyl} GURICHIRURETINATO.

[0013] The derivative expressed with the general formula (1) of this invention can be manufactured by the following reaction formulae (A).

[0014]

[Formula 3]



[0015] Namely, dissolve in solvents, such as a desiccation pyridine, and DMC (2-chloro-1,3-dimethylimidazolinium chloride) etc. is used. Under 4-dimethylaminopyridine existence or nonexistence, or chloroform, N,N'-dicyclohexylcarbodiimide etc. is used among solvents, such as dichloromethane. Or bases, such as 1-ethyl-3-(3'-dimethylaminopropyl) carbodiimide hydro chloride and triethylamine, are used among solvents, such as chloroform and dichloromethane. Or the compound which the alcohol expressed with glycyrrhetic acid and general formula R1 OH using the bottom carbonyldiimidazole of base existence etc. is made to react, and is expressed with a general formula (2) is obtained. Next, the compound expressed with a general formula (2) is dissolved in solvents, such as desiccation dichloromethane. Under a dry light and silver carbonate existence The hydroxyl group of the 1st place of what (disaccharide) the lactose derivative etc. condensed general formula R3 X[R3 X Fluorine, chlorine -- SHUU -- base -- etc. -- a halogen -- an atom -- (X) -- permuting -- having -- others -- a hydroxyl group -- all -- an acetyl group -- etc. -- a protective group -- protecting -- having -- **** -- a compound -- being shown --] -- expressing -- having -- sugar -- a compound -- reacting -- making -- the compound of a formula (3) -- obtaining .

[0016] Further, the compound of a formula (3) is made to react by organic bases, such as inorganic bases, such as the inside of alcohols solvents, such as water, a methanol, ethanol, and propanol, or those partially aromatic solvents, a sodium hydroxide, a potassium hydroxide, a sodium carbonate, potassium carbonate, a sodium hydrogencarbonate, and a potassium hydrogencarbonate, or aqueous ammonia, monomethylamine, ethylamine, dimethylamine, diethylamine, a trimethylamine, and triethylamine, and is R3. Deprotection of the protective group is carried out and the compound of a formula (4) is obtained. R4 It is the residue of disaccharide (lactose). The compound of a formula (4) is dissolved in solvents, such as a desiccation pyridine. Under protection from light or un-shading Next, a sulfuric anhydride-pyridine complex, A chlorosulfonic acid etc. is made to react. Further Or LiOH, NaOH, adjusting pH of reaction mixture with solutions, such as hydroxylation alkali metal, such as KOH, or Mg(OH)2, and a hydroxylation alkaline-earth-metal compound of calcium(OH)2 grade, -- all the hydroxyl groups of sugar -- SO3 M (M -- a

hydrogen atom --) Or the compound of the formula (1) which alkali metal and an alkaline-earth-metal atom combined is obtained.

[0017] In manufacture from the above-mentioned glycyrrhetic acid to the compound of a formula (1), not only the solvent indicated above as a solvent but a hexane, benzene, toluene, a carbon tetrachloride, chloroform, dichloromethane, diethylether, diisopropyl ether, ethyl acetate, methyl acetate, a tetrahydrofuran, dioxane, a methanol, ethanol, propanol, isopropanol, dimethyl sulfoxide, N.N-dimethylformamide, N,N-dimethylacetamide, water, and those partially aromatic solvents can react.

[0018] Especially a limit does not have temperature, and it is near the boiling point of under ice-cooling to a solvent, and reacts [preferably] to the bottom of protection from light if needed for one - two days at a room temperature. As processing after a reaction, according to the usual technique, a ** exception, reaction mixture, or a filtrate is poured out for settling into iced water if needed, reaction mixture is dissolved in solvents, such as ethyl acetate, diethylether, a tetrahydrofuran, dichloromethane, chloroform, toluene, benzene, and a xylene, and a base or water, such as acids, such as dilute hydrochloric acid, a dilute sulfuric acid, and aqua fortis, or a rare sodium-hydroxide water solution, a rare sodium-carbonate water solution, a rare potassium-hydrogencarbonate water solution, and rare aqueous ammonia, washes. drying agents, such as after washing, sulfuric anhydride magnesium, and anhydrous sodium sulfate, -- desiccation and a drying agent -- after [according to **] and a filtrate -- the need -- responding -- the bottom of reduced pressure -- or it condenses under ordinary pressure.

[0019] The concentration residue obtained as a purification method Silica gel, an alumina, a silicious marl, etc., The bulking agent which embellished them with various coating agents is used. Or under the pressure of ordinary pressure to hundreds atmospheric pressures, It applies to the column chromatography of a sequential layer or an inversional layer. A hexane, toluene, The ether, ethyl acetate, methyl acetate, dichloromethane, chloroform, An acetone, a tetrahydrofuran, dioxane, ethanol, a methanol, Water, an acetic acid, dimethyl sulfoxide, N.N-dimethylformamide, It carries out combining recrystallization, reprecipitation, or those approaches using the approach eluted with mixed solvents of those suitable ratios, such as triethylamine and aqueous ammonia, the same solvent, or the mixed solvent of those suitable ratios.

[0020] When this compound is used as an anti-AIDS virus agent, it mixes with independent, an excipient, or support, and a medicine is prescribed for the patient as injections, an oral agent, or suppositories. What is permitted in pharmaceutics as an excipient and support is chosen, and the class and presentation are decided with a route of administration or a medication method. For example, animal and vegetable oils or synthetic oil, such as water, alcohols or soybean oil, a peanut oil, sesame oil, and a mineral oil, is used as liquefied support, and organic-acid salts, such as cellulosics, such as saccharides, such as a lactose, a maltose, and sucrose, amino acid, and hydroxypropylcellulose, and magnesium stearate, etc. are used as a solid support.

[0021] Although the excipients used by injections are a mannitol, a maltose, a dextran, a lactose, cyclodextrin, chondroitin sulfate, gelatin, and a human serum albumin, a maltose, a lactose, chondroitin sulfate, gelatin, and a human serum albumin are desirable. It considers as lyophilized products with these excipients, and at the time of administration, it can dissolve in liquids for vein administration, such as the suitable solvent for injection, for example, sterilized water, a physiological saline, grape-sugar liquid, and electrolytic solution hydrolyzed vegetable protein, and it can also be prescribed for the patient. Moreover, the buffer of an acid, alkali, or optimum dose may be added for the purpose, such as pH adjustment, during the presentation of the pharmaceutical preparation in this invention.

[0022] Although the content of this compound in pharmaceutical preparation changes variously with pharmaceutical preparation, it is usually 1 - 98 % of the weight preferably 0.1 to 100% of the weight. For example, in the case of a parenteral solution, it is usually good to make it 1 - 10% of the weight of an active principle included preferably 0.1 to 30% of the weight. When administering orally, it is used with said solid support or liquefied support with gestalten, such as a tablet, a capsule, powder material, a granule, liquids and solutions, and dry-syrups. Generally a capsule, a tablet, granulation, and powder material contain 25 - 98% of the weight of an active principle preferably five to 100% of the weight. Although a dose is determined by a patient's age, weight, a symptom, the therapy purpose, etc., generally therapeutic doses are 5 - 500 mg/kg and a day in 1 - 100 mg/kg and a day, and internal use at parenteral administration. This compound is low toxicity comparatively, and it is the description that accumulative [by repetitive administration / toxic] is small.

[0023]

[Function] The example of a trial shows the effectiveness that this invention compound checks infection of HIV.

Example of a trial Activity test method for HIV of this invention compound (the IFA method)

Anti-HIV activity evaluation was performed according to the approach of Hoshino and others (notes). After adding the test compound of the various concentration of 50microl into MT-4 cell (0.5x105 cells / 0.5ml) wound around 48 hole plate and incubating into it for 2 hours, HIV (5x104 - 1x105 PFU/ml) of 50microl was infected. After collecting some cells about each hole four days after and fixing with the acetone on the slide glass, the rate of the cell used as a HIV antigen positivity was judged with the indirect fluorescent antibody technique (the blood serum of an AIDS patient was used as a primary antibody, and fluorescein isothiocyanate (FITC) indicator anti-Homo sapiens IgG was used as a secondary antibody). (notes . THE JOURNAL OF ANTIBIOTICS Vol.40.No.7.pp1077-1078July 1988, ANTIMICROBIAL AGENTS AND CHEMOTHERAPY Vol.33, No.5, May 1989.p773-775) A result is shown in Table 1.

[0024]

[Table 1]

Table 1: Activity over AIDS virus (HIV) by IFA method Compound number A HIV antigen positivity cell (%) EC50 (mug/ml) (Cytotoxicity: - - +++) (mug/ml) 1 10 100 1000 Glycyrrhizin > 90 > 90 > 90 < 1 500 (-) (-) (-)

Glycyrrhizin > 90 > 90 80 < 1 440 sulfation object NATORIU (-) (-) (-) (-)

A MU salt compound (1) > 90 10 < 1 x 5.5 (-) (-) (-) (+++) Compound (6) 80 5 < 1 x 4.6 (-) (-) (-) (+++)

Compound (11) > 90 25 < 1 x 6.5 (-) (-) (-) (+++) Compound (13) > 90 80 < 1 x 44 (-) (-) (-) (+++) Control : [90%,] x: Judgment impossible glycyrrhizin sulfation object sodium salt: 3-O-{2, 3, 4-Tori (sodium sulfonate) beta-D-glucuronopyranosyl (1->2) -3, and 4-JI (sodium sulfonate)-beta-D-glucuronopyranosyl} glycyrrhizin [0025]

[Example] Next, an example explains this invention concretely.

(1) Esterification reaction (glycyrrhetic acid -> compound of a formula (2))

Example 1 Undecyl The synthetic glycyrrhetic acid (5g) of GURICHIRURETINATO (14) and (formula (2):R1 = undecyl) is melted to dry pyridine, and they are n-undecyl alcohol (5ml) and DMC (3.6g). In addition, it stirred at the room temperature for 24 hours. The residue which carried out sequential washing with HCl, a saturation sodium bicarbonate water solution, and water 5% after the extract by CH2Cl2, and obtained reaction mixture with vacuum concentration after desiccation is given to a column chromatography (benzene-acetone, gradient up to 2.0%), and it is a compound (14) (4.7g, yield 71.2%). It obtained.

[0026] EI-MS m/z (rel. intensity): 624 (M+), 607(19), 606(34), 592(15), 563(17), 458(29), 457(72), 417 (18), 416(35), 217(20), 216(14), 192(10), 189(37), 175(44), 174(12), 173(18), 161(15), 159(12), 149(20), 148(11), 147(17), 145(10), 136(13), 135(100). 1H-NMR (CDCl3) delta: 0.81, 0.81, and 1.01, 1.13, 1.14, 1.15, and 1.37 (each 3H, s, CH3) 0.88 1.26 (3H, t, J= 7.0Hz, -CH2CH3) 2.34 (18H, s, -CH2-x 9) (1H, s, H-9), 2.79 (1H and broad d -- J= 13.6Hz) H-18 3.23 () [1H, dd,] [J=10.3] and 5.9Hz and H-3 4.09 (2H, t, J= 7.0Hz, -COOCH2-) 5.65. (1H, s, H-12) Anal. Calcd for C41H68O4 : C, 78.79 ; H, 10.97. Found : C, 78.83; H, 10.77. DMC : 2-chloro -1, 3-dimethyl imidazolinium chloride [0027] Example 2 Hexyl The synthetic glycyrrhetic acid (15g) of GURICHIRURETINATO (15) and (formula (2) R1 = hexyl) is melted to dry pyridine, and they are n-hexyl alcohol (8ml) and DMC (10.8g). In addition, it stirred at the room temperature for 24 hours. An extract is doubled for reaction mixture after an extract by CH2Cl2 (150mlx3), and it is HCl 5%, It is a column chromatography (benzene-acetone, gradient up to 4.0%) about the residue which carried out sequential washing with a saturation sodium bicarbonate water solution and water and which was obtained with vacuum concentration after desiccation on magnesium sulfate. It gave and a compound (15), and (14.8g and yield 83.7%) were obtained.

[0028] EI-MS m/z (rel. intensity): 554 (M+), 537(15), 536(34), 521(21), 493(23), 388(16), 387(46), 346 (34), 217(21), 216(14), 201(11), 189(35), 187(11), 175(39), 174(14), 173(20), 161(18), 159(14), 149(20), 148(13), 147(20), 145(11), 136(12), 135(100). 1H-NMR (CDCl3) delta: 0.81, 0.81, and 1.01, 1.13, 1.14, 1.15, and 1.37 (each 3H, s, CH3) 0.89 1.33 (3H, t, J= 6.6Hz, -CH2CH3) 2.34 (8H, s, -CH2-x 4) (1H, s, H-9), 2.79 (1H and broad d -- J= 13.6Hz) H-18 3.22 () [1H, dd,] [J=10.3] and 5.9Hz and H-3 4.09 (2H, t, J= 6.6Hz, -COOCH2-) 5.65. (1H, s, H-12) Anal. Calcd for C36H58O4 : C, 77.93 ; H, 10.54. Found : C, 71.81; H, 10.35. [0029] Example 3 Octadecyl The synthetic GURICHIN retinoic acid (50g) of

GURICHIRURETINATO (16) and (formula (2) R1 = octadecyl) was melted to dry pyridine, 1-OKUTA decanol (60g) and DMC (36g) were added, and it stirred at the room temperature for 24 hours. It is a column chromatography (benzene-acetone, gradient up to 2.0%) about the residue which doubled the extract after the extract by CH2Cl2 (150mlx3), carried out sequential washing with HCl, a saturation sodium bicarbonate water solution, and water 5%, and obtained reaction mixture with vacuum concentration after desiccation on magnesium sulfate. It gave and a compound (16), and (57.9g and yield 74.4%) were obtained.

[0030] FAB-MS (m/z) 745 [M+Na] + 1 H-NMR (CDCl3) delta: 0.81, 0.81, 1.01, 1.13, and 1.14, 1.15 and

1.37 (each 3H, s, CH3) 0.88 1.25 (3H, t, $J= 6.6\text{Hz}$, -CH2CH3) 2.34 (32H, s, -CH2-x16) (1H, s, H-9), 2.80 (1H and broad d -- $J= 13.6\text{Hz}$) H-18 3.23 () [1H, dd,] [$J=9.9$] and 5.9Hz and H-3 4.09 (2H, t, $J= 7.0\text{Hz}$, -COOCH2-) 5.65.(1H, s, H-12) Anal.Calcd for C48H82O4 : C, 79.72; H, 11.43. Found : C and 79.58 ; H, 11.49. [0031] (2) Glycosylation reaction (the compound of a formula (2) -> compound of a formula (3)) Example 4. Synthetic compound of a compound (18), and (formula (3);R1 = undecyl and R3 = hepta--O-acetyl-lactosyl) (14) (1.8g) Melt to dry CH2Cl2 and a container is shaded. Drierite (1g) and Ag2CO3 (3g) are added, and they are after 1-hour stirring and a hepta--O-acetyl-lactosyl-star's picture (6.5g). In addition, it stirred for two days at the room temperature further. The filtrate was poured in into iced water (100ml) after filtering reaction mixture, the extract and the extract were doubled by CH2Cl2 (80ml x3), sequential washing was carried out with saturation sodium bicarbonate water and water, and it dried on magnesium sulfate. It is a column chromatography (benzene-EtOAc, gradient up to 4%) about the residue which condensed and obtained the filtrate after filtration. And high-performance-chromatography HPLC [ODS 10mm x250mm (MeOH)] was performed, and a compound (18), and (1.8g and yield 50.3%) were obtained after purification.

[0032] FAB-MS1265 (m/z) [M+Na]+Anal.Calcd for C67H102O21 C, 64.71 ; H, 8.27. Found : C, 64.36 ; H, the 8.40.1 H-NMR (CDCl3) aglycon Me 1.35, 1.14, 1.12, 1.11, 0.92, 0.80, 0.76(each s) COOCH2 4.08 (CH2 (t, $J= 6.2\text{Hz}$)) 1.26 CH(s, 18H)2CH3 0.88 H(t, $J= 6.2\text{Hz}$)-3 3.08 H(t, $J= 8.4\text{Hz}$)-9 2.31 (s) H-12 5.65 (s) H-18 2.79 Inner (broad d, $J= 13.6\text{Hz}$) sugar H-1 4.47 H(d, $J= 8.1\text{Hz}$)-2 4.94 H(dd, $J= 9.2, 8.1\text{Hz}$)-3 5.19 H(t, $J= 9.2\text{Hz}$)-4 3.72 H(t, $J= 9.2\text{Hz}$)-5 3.60 H(dd, $J= 9.2, 6.2, 1.8\text{Hz}$)-64.41 H(dd, $J= 11.7, 1.8\text{Hz}$)-6' 4.06-4.16 outer (overlapped) sugar H-1 4.50 H(d, $J= 7.7\text{Hz}$)-2 5.11 H(dd, $J= 10.3, 7.7\text{Hz}$)-3 4.95 H(dd, $J= 10.3, 2.6\text{Hz}$)-4 5.34 H(d, $J= 2.6\text{Hz}$)-5 3.88 H(t, $J= 6.6\text{Hz}$)-6 4.04 - 4.16 H(overlapped)-6' 4.04 - 4.16 Ac (overlapped) 2.15, 2.09, 2.06, 2.05, 2.04, 2.02, 1.96 (each s) [0033] Example 5 Synthetic methyl of a compound (20), and (formula (3);R1 = methyl and R3 = hepta--O-acetyl-lactosyl)

GURICHIRURETINATO (19) (2.0g) Melt to dry CH2Cl2 and a container is shaded. Drierite (1g) and Ag2CO3 (4.5g) -- adding -- after 1-hour stirring and a hepta--O-acetyl-lactosyl-star's picture (11.0g) -- in addition, it stirred for two days at the room temperature further. A filtrate is poured in into iced water (100ml) after filtering reaction mixture, and it extracts by CH2Cl2 (80ml x3). The extract was doubled, sequential washing was carried out with saturation sodium bicarbonate water and water, and it dried on magnesium sulfate. A column chromatography (benzene-EtOAc, gradient up to 4.0%) and high-performance-chromatography HPLC [ODS 10mm x250mm (MeOH)] are performed for the residue which condensed and obtained the filtrate after filtration, and they are after purification and a compound (20) (2.6g, yield 57.0%). It obtained.

[0034] mp.214-215 **FAB-MS1125 (m/z) [M+Na]+1 H-NMR (CDCl3) Aglycon Me 1.36, 1.14, 1.12, 1.12, 0.93, 0.81, 0.76(each s) COOCH3 3.96 (s) H-3 3.09 H(t, $J= 7.9\text{Hz}$)-9 2.31 (s) H-12 5.65 (s) H-18 2.78 Inner (broad d, $J= 11.4\text{Hz}$) sugar H-1 4.52 H(d, $J= 8.1\text{Hz}$)-2 4.93 H(dd, $J= 9.5, 8.1\text{Hz}$)-3 5.19 H(t, $J= 9.5\text{Hz}$)-4 3.74 H(t, $J= 9.5\text{Hz}$)-5 3.65 H(dd, $J= 9.5, 6.6, 1.8\text{Hz}$)-6 4.42 H(dd, $J= 11.0, 1.8\text{Hz}$)-6' 4.05-4.16 outer (overlapped) sugar H-1 4.52 H(d, $J= 8.1\text{Hz}$)-2 5.10 H(dd, $J= 10.3, 8.1\text{Hz}$)-3 4.97 H(dd, $J= 10.3, 3.3\text{Hz}$)-4 5.34 H(t, $J= 3.3\text{Hz}$)-5 3.92 H(t, $J= 6.6\text{Hz}$)-6 4.05 - 4.16 H(overlapped)-6' 4.05 - 4.16 Ac (overlapped) 2.15, 2.18, 2.06, and 2.05, 2.04, 2.02, 1.98(each s) Anal.Calcd for C57H82O21:C, 62.05 ; H, 7.49. Found : C, 62.23 ; H, 7.43. [0035] Example 6. compound (21) (formula (3);R1 = hexyl, R3 = hepta--O-acetyl-lactosyl) Synthetic compound (15) (2.0g) Melt to dry CH2Cl2 and a container is shaded. Drierite (1g) It reaches, Ag2CO3 (3.5g) is added, and they are after 1-hour stirring and a hepta--O-acetyl-lactosyl-star's picture (9.0g). In addition, it stirred for two days at the room temperature further. A filtrate is poured in into iced water (100ml) after filtering reaction mixture, and it extracts by CH2Cl2 (80ml x3). The extract was doubled, sequential washing was carried out with saturation sodium bicarbonate water and water, and it dried on magnesium sulfate. It is a column chromatography (benzene-EtOAc, gradient up to 8%) about the residue which condensed and obtained the filtrate after filtration. And high-performance-chromatography HPLC [ODS 10mm x250mm (MeOH)] is performed, and they are after purification and a compound (21) (2.3g, yield 52.0%). It obtained.

[0036] FAB-MS1195 (m/z) [M+Na]+Anal.Calcd for C62H92O21 C, 63.46 ; H, 7.90. Found : C, 63.29 ; H, the 8.21.1 H-NMR (CDCl3) aglycon Me 1.35, 1.33, 1.14, 1.12, 0.92, 0.80, 0.75(each s) COOCH2 4.04-4.16 (CH2 (overlapped)) 1.32 CH(s, 8H)2CH3 0.89 H(t, $J= 6.6\text{Hz}$)-3 3.08 H(t, $J= 8.1\text{Hz}$)-9 2.31 (s) H-12 5.64 (s) H-18 2.79 Inner (broad d, $J= 13.6\text{Hz}$) sugar H-1 4.48 H(d, $J= 7.7\text{Hz}$)-2 4.93 H(dd, $J= 9.5, 7.7\text{Hz}$)-3 5.19 H(t, $J= 9.5\text{Hz}$)-4 3.72 H(t, $J= 9.5\text{Hz}$)-5 3.61 H(dd, $J= 9.5, 5.9, 1.8\text{Hz}$)-64.42 H(dd, $J= 11.7, 1.8\text{Hz}$)-6' 4.04-4.16 outer (overlapped) sugar H-14.51 H(d, $J= 8.1\text{Hz}$)-2 5.11 H(dd, $J= 10.6, 8.1\text{Hz}$)-3 4.95 H(dd, $J= 10.6, 3.3\text{Hz}$)-4 5.35 H(t, $J= 3.3\text{Hz}$)-5 3.88 H(t, $J= 6.6\text{Hz}$)-6 4.04 - 4.16 H(overlapped)-6' 4.04 - 4.16 Ac

(overlapped) 2.15, 2.09, 2.06, 2.05, 2.04, 2.02, 1.96 (each s) [0037] Synthetic compound of an example 7. compound (22), and (formula (3);R1 = octadecyl and R3 = hepta--O-acetyl-lactosyl) (16) (2.0g) Melt to dry CH₂Cl₂ and a container is shaded. Drierite (1g) It reaches, Ag₂CO₃ (3.5g) is added, and they are after 1-hour stirring and a hepta--O-acetyl-lactosyl-star's picture (7.3g). In addition, it stirred for two days at the room temperature further. A filtrate is poured in into iced water (100ml) after filtering reaction mixture, and it extracts by CH₂Cl₂ (80ml x3). The extract was doubled, sequential washing was carried out with saturation sodium bicarbonate water and water, and it dried on magnesium sulfate. It is a column chromatography (benzene-EtOAc, gradient up to 4%) about the residue which condensed and obtained the filtrate after filtration. And high-performance-chromatography HPLC [ODS 10mmx250mm (MeOH)] is performed, and they are after purification and a compound (22) (1.5g, yield 40.4%). It obtained.

[0038] FAB-MS 1363 (m/z) [M+Na]⁺Anal. Calcd for C₇₄H₁₁₆O₂₁ C, 66.24 ; H, 8.71. Found : C, 66.36 ; H, the 8.65. 1 H-NMR (CDCl₃) aglycon Me 1.35, 1.14, 1.12, 1.12, 0.92, 0.80, 0.76 (each s) COOCH₂ 4.08 (CH₂ (t, J= 6.2Hz)) 1.25 CH(s, 32H) 2CH₃ 0.88 H(t, J= 6.2Hz)-3 3.08 H(t, J= 8.1Hz)-9 2.31 (s) H-12 5.64 (s) H-18 2.79 Inner (broad d, J= 13.2Hz) sugar H-1 4.48 H(d, J= 7.7Hz)-2 4.93 H(dd, J= 9.5, 7.7Hz)-3 5.19 H(t, J= 9.5Hz)-4 3.72 H(t, J= 9.5Hz)-5 3.60 H(ddd, J= 9.5, 6.2, 1.8Hz)-64.41 H(dd, J= 11.7, 1.8Hz)-6' 4.04-4.16 outer (overlapped) sugar H-1 4.50 H(d, J= 7.3Hz)-2 5.10 H(dd, J= 10.3, 7.3Hz)-3 4.95 H(dd, J= 10.3, 2.9Hz)-4 5.34 H(t, J= 2.9Hz)-5 3.88 H(t, J= 6.3Hz)-6 4.04 - 4.16 H(overlapped)-6' 4.04 - 4.16 Ac (overlapped) 2.15, 2.09, 2.06, 2.05, 2.04, 2.02, 1.96 (each s) [0039] (3) Deprotection radical reaction (the compound of a formula (3) -> compound of a formula (4))

Example 8. compound (23); URUDESHIRU 3-O- {beta-D-galactopyranosyl (1->4)-beta-D-glucopyranosyl} GURICHIRURETINATO synthetic compound (18) (1.5g) It melts to KOH in EtOH-H₂O (25 (1:1)ml) 5%. After carrying out 1 evening gentle placement, an after [purification] compound (23), and (820mg and yield 70.9%) were obtained for the residue which neutralized and carried out vacuum concentration and which was obtained with the acetic acid with the column chromatography (CHCl₃:MeOH:H₂O=65:35:20 - 10 lower phase).

[alpha] 25D+58.4 (c= 1.0, pyridine) FAB-MS m/z : 971 [M+Na]⁺Anal. Calcd for C₅₃H₈₈O_{14.1/2}H₂O : C, 66.29 ; H, 9.54. Found C, 66.38 ; H, 9.36 [0040] 13C-NMR(C₅D₅N) delta : An aglycon C-1 39.52 26.43 88.74 39.85 55.46 17.67 32.98 44.29 61.910 37.311 199.312 128.713 169.014 45.515 26.616 26.517 32.118 48.719 41.320 43.421 31.422 38.223 28.224 16.725 17.026 18.827 23.528 28.729 29.130176.4-OCH₂-64.6-CH₃- 14.3-CH₂- 32.129.8 x229.729.529.428.326.722.9 inner sugar C-1105.7275.23 77.14 82.55 76.86 62.5 outer sugar C-1 106.42 75.13 72.54 69.95 76.16 62.1 spectrum is measured in a heavy pyridine (C₅D₅N).

[0041] Example 9. compound (24); methyl 3-O- {beta-D-galactopyranosyl (1->4)-beta-D-glucopyranosyl} GURICHIRURETINATO synthetic compound (20) (1.8g) It melts to KOH in EtOH-H₂O (35 (1:1)ml) 5%. After carrying out 1 evening gentle placement, an after [purification] compound (24), and (1.1mg and yield 82.7g) were obtained for the residue which neutralized and carried out vacuum concentration and which was obtained with the acetic acid with the column chromatography (CHCl₃:MeOH:H₂O=65:35:20 - 10 lower phase).

[alpha] 20D+87.3 (c= 1.0, pyridine) FAB-MS m/z : 831 [M+Na]⁺Anal. Calcd for C₄₃H₆₈O_{14.1/2}H₂O : C, 63.14 ; H, 8.50. Found C, 63.24 ; H, 8.38 [0042] 13C-NMR(C₅D₅N) delta : An aglycon C-1 42.52 29.63 91.84 42.95 54.86 20.77 35.98 47.29 65.010 40.311 202.612 131.713 172.214 48.615 29.816 26.517 35.118 51.719 44.320 46.421 34.322 41.223 31.224 19.825 20.126 21.827 24.528 31.229 31.630179.9-OCH₃ 68.4 inner sugar C-1 108.82 78.33 80.14 85.55 79.96 65.5 outer sugar C-1 109.5278.23 75.54 73.05 79.26 65.1

[0043] Example 10. Compound (25); hexyl 3-O- {beta-D-galactopyranosyl (1->4)-beta-D-glucopyranosyl} GURICHIRURETINATO synthetic compound (21) (1.6g) It melts to KOH in EtOH-H₂O (30 (1:1)ml) 5%. It is a compound after purification (25) (1.0g, yield 82.5%) with a column chromatography (CHCl₃:MeOH:H₂O=65:35:20 - 10 lower phase) about the residue which neutralized and carried out vacuum concentration and which was obtained with the acetic acid after carrying out 1 evening gentle placement. It obtained.

[alpha] 20D+81.9 (c= 1.0, pyridine) FAB-MS m/z : 901 [M+Na]⁺Anal. Calcd for C₄₃H₇₈O_{14.1/2}H₂O : C, 64.91 ; H, 8.97. Found C, 64.94 ; H, 8.86 [0044] 13C-NMR(C₅D₅N) delta : An aglycon C-1 39.4 2 26.53 88.74 39.85 55.36 17.67 32.98 44.29 61.910 37.211 199.412 128.613 169.214 45.515 26.716 25.917 32.018 48.719 41.320 43.421 31.32228.123 28.324 16.725 17.026 18.827 23.428 28.129 28.730 176.4-OCH₂-64.5-CH₃ 14.1-CH₂- 31.529.022.7 x2 inner sugar C-1 105.7275.13 77.14 82.35 76.86 62.3 outer sugar C-1 106.4275.13 72.44 69.95 76.16 62.1 [0045] example 11 compound (26); -- octadecyl 3-O- {beta-D-galactopyranosyl (1->4)-beta-D-glucopyranosyl} GURICHIRURETINATO synthetic compound (22) (1.2g)

It melts to KOH in EtOH-H₂O (25 (1:1)ml) 5%. It is a compound after purification (26) (765mg, yield 81.0%) with a column chromatography (CHCl₃:MeOH:H₂O=65:35:20 - 10 lower phase) about the residue which neutralized and carried out vacuum concentration and which was obtained with the acetic acid after carrying out 1 evening gentle placement. It obtained.

[alpha] : 1069 [M+Na] + Anal. Calcd for C₆₀H₁₀₂O₁₄.1/2 H₂O : C, 68.21 ; 20D+55.3(c= 1.0, pyridine) mp.246 - 247 **FAB-MS m/z H, 9.84. Found C, 67.87 : H, 9.62. [0046] ¹³C-NMR(C₅D₅N) delta : An aglycon C-1 39.32 26.53 88.74 39.75 55.36 17.57 32.88 44.09 61.710 37.111 199.212 128.613 168.814 45.415 26.616 26.217 32.018 48.519 41.220 43.321 31.222 38.023 28.324 16.625 16.826 18.727 23.428 28.629 28.930 176.1-OCH₂- 64.4-CH₃ 14.2-CH₂- 31.929.8 x429.7 x329.629.529.328.926.322.8 inner sugar C-1 105.4274.73 76.74 82.15 76.46 76.2 outer sugar C-1 106.12 74.73 72.04 69.75 75.76 61.9[0047] (4)

Sulfation reaction (the compound of a formula (4) -> compound of a formula (1))

an example 12 and compound (11); undecyl 3-O-{2, 3 and 4, 6-tetrapod (sodium sulfonate)-beta-D-galactopyranosyl (1->4) - 2, 3, 6-Tori (sodium sulfonate)-beta-D-glucopyranosyl}

GURICHIRURETINATO synthetic compound (23), and (500mg) dry pyridine (8ml) It melted, the container was shaded, SO₃-Pyridine Complex (1.8g) was added, and it stirred at the room temperature for 24 hours. It is 1M NaOH about pH of reaction mixture. pH 8-9 It adjusts and is H₂O-MeOH (1:1) (30ml). Vacuum concentration was diluted and carried out and residue was obtained. Water solution of this residue (5ml) It rinses, after making it give and stick to Diaion HP-20, and it is MeOH (150ml) 50%. It is eluted and is a compound (11) (673mg yield 75.9%). It obtained.

[alpha] 20D+32.4 degree(c= 1.0, H₂O) FAB-MS m/z:1685 [M+Na] + [0048] ¹³C-NMR(D₂O) (internal standard matter dioxane) delta : An aglycon C-1 41.12 29.43 93.14 41.75 56.56 18.87 35.18 46.69 56.910 39.111 204.912 130.413 173.614 48.015 29.416 28.717 34.218 50.519 43.020 45.821 33.522 40.923 31.124 17.625 18.326 21.327 25.328 30.129 31.930 180.2-OCH₂- 67.1-CH₃ 16.5-CH₂- 34.4 x232.3 x331.325.1 x221.6 inner sugar C-1 102.9275.83 80.14 82.15 77.96 64.0 outer sugar C-1 105.52 74.53 69.74 68.25 77.76 64.0[0049] example 13. compound (1); -- methyl 3-O-{2, 3 and 4, 6-tetrapod (sodium sulfonate)-beta-D-galactopyranosyl (1->4) - 2, 3, 6-Tori (sodium sulfonate)-beta-D-glucopyranosyl}

GURICHIRURETINATO synthetic compound (24), and (500mg) dry pyridine (8ml) It melted, the container was shaded, SO₃-Pyridine Complex (2.1g) was added, and it stirred at the room temperature for 24 hours. It is 1M NaOH about pH of reaction mixture. pH 8-9 It adjusts and is H₂O-MeOH (1:1) (30ml). Vacuum concentration was diluted and carried out and residue was obtained. Water solution of this residue (5ml) It rinses, after making it give and stick to Diaion HP-20, and it is MeOH (150ml) 50%. It was eluted and a compound (1) and (806mg yield 84.6%) were obtained.

[0050] [alpha] 20D+57.3 (c= 1.0, H₂O) FAB-MS m/z:1545 [M+Na]+13C-NMR (D₂O); (internal standard matter dioxane)

An aglycon C-1 39.62 27.23 91.54 39.95 55.46 18.07 33.38 44.99 58.310 37.311 203.512 128.513 172.714 46.315 27.216 26.317 32.518 49.119 41.420 44.121 31.522 38.923 27.824 16.625 17.026 19.627 23.628 28.429 29.530 179.8-OCH₃ The 53.2 inner sugar C-1 101.2274.13 78.34 80.55 76.26 62.4 outer sugar C-1 103.82 72.93 68.14 66.75 76.06 62.4 [0051] example 14. compound (6); -- hexyl A 3-O-{2, 3, 4, 6-tetrapod (sodium sulfonate)-beta-D-galactopyranosyl (1->4) -2, and 3-6-Tori (sodium sulfonate)-beta-D-glucopyranosyl} GURICHIRURETINATO synthetic compound (25) and (500mg) dry pyridine (8ml) It melted, the container was shaded, SO₃-Pyridine Complex (1.9g) was added, and it stirred at the room temperature for 24 hours. It is 1M NaOH about pH of reaction mixture. pH 8-9 It adjusts and is H₂O-MeOH (1:1) (30ml). Vacuum concentration was diluted and carried out and residue was obtained. Water solution of this residue (5ml) It rinses, after making it give and stick to Diaion HP-20, and it is MeOH (150ml) 50%. It is eluted and is a compound (6) (672mg, yield 73.3%). It obtained.

[0052] [alpha] 20D+46.0 (c= 1.0, H₂O) FAB-MS m/z:1615 [M+Na]+13 C-NMR(D₂O);(internal standard matter dioxane) delta : [Aglycon C-1] 39.62 27.23 91.54 39.95 55.36 17.77 33.38 44.89 58.210 37.411 202.912 128.713 171.714 46.315 27.216 26.417 32.518 48.919 41.420 44.121 31.722 39.123 28.424 16.625 17.026 19.627 23.528 27.729 29.330 178.2-OCH₂- 65.5-CH₃ 14.7-CH₂- 32.029.623.2 x2 inner sugar C-1 1101.32 74.13 78.34 80.55 76.36 62.4 outer sugar C-1 103.72 72.93 68.04 66.75 76.06 62.4 [0053] example 15. compound (13); -- octadecyl 3-O-{2, 3 and 4, 6-tetrapod (sodium sulfonate)-beta-D galactopyranosyl (1->4) - 2, 3, 6-Tori (sodium sulfonate)-beta-D-glucopyranosyl} GURICHIRURETINATO synthetic compound (26), and (500mg) dry pyridine (8ml) It melted, the container was shaded, SO₃-Pyridine Complex (1.3g) was added, and it stirred at the room temperature for 24 hours. It is 1M NaOH about pH of reaction mixture. pH 8-9 It adjusts and is H₂O-MeOH (1:1) (30ml). Vacuum concentration was diluted and carried out and residue was obtained. Water solution of this residue (5ml) To Diaion HP-20, through and

after making it adsorb, it rinses, and it is MeOH (150ml) 50%. It is eluted and is a compound (13) (683mg, yield 80.4%). It obtained.

[0054] [alpha] 20D+35.8 (c= 1.0, H₂O) 13C-NMR(D₂O);(internal standard matter dioxane) delta : [Aglycon C-1] 39.52 27.33 91.44 40.05 55.16 18.17 33.38 44.99 58.310 37.411 202.912 128.813 171.414 46.215 27.316 27.017 32.518 48.819 41.220 44.121 31.722 39.223 28.524 16.725 17.126 19.627 23.628 27.729 29.530178.2-OCH₂- 65.3-CH₃ 14.7-CH₂- 23.4 x229.630.2 x230.5 x530.6 x432.7 x2 inner sugar C-1 101.32 74.13 78.54 80.45 76.36 62.3 outer sugar C-1 103.72 72.93 68.04 66.65 76.36 62.2 [0055] The drug solution 500 weight section adjusted to pH4.0 with the example 16 injections compound number 6, 10 weight sections, the lactose 20 weight section, 1N-hydrochloric acid, and distilled water for injection (optimum dose) is obtained. After carrying out disinfection filtration of this adjusted drug solution with a membrane filter, it pours distributively and freeze-dries to the glassware for injection. The pharmaceutical preparation for freeze-drying injection which contains the compound number 6 (100mg) in one vial is obtained after freeze-drying termination.

[0056] Example 17 granule compound number 6 It mixed with 50 weight sections, the lactose 600 section, the crystalline cellulose 330 section, and the hydroxypropylcellulose 20 section well, screening was carried out so that it might compress and crush using a roll mold compressor (roller compactor trademark) and might enter between 16 meshes and 60 meshes, and it considered as granulation.

[0058] Example 18 tablet compound number 6 30 weight sections, the crystal lactose 120 section, the crystalline cellulose 147 section, and the magnesium stearate 3 section were tableted after mixing by the V shaped rotary mixer, and the tablet with one lock of 300mg was obtained.

[0058]

[Effect of the Invention] The glycyrrhetic acid related compound of this invention shows the dozens to hundreds times as many outstanding inhibition effectiveness of glycyrrhizin and glycyrrhizin sulfation object sodium salt as this to infection of HIV, and its safety is [toxicity is also low and] also useful by the high thing as an active principle of a Homo sapiens acquired-immune-deficiency-syndrome viral infection inhibitor.

[Translation done.]

PATENT ABSTRACTS OF JAPAN

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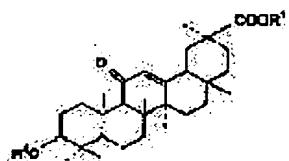
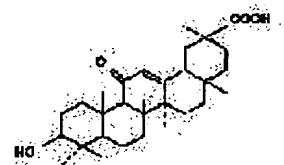
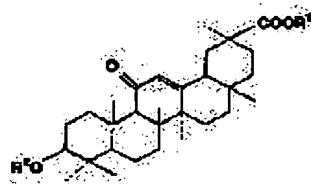
(21) Application number : 05-252140 (71) Applicant : NIPPON KAYAKU CO LTD
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 HOSHINO KOUROU
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(54) NOVEL GLYCYRRHETIC ACID-RELATED COMPOUNDS OF THEIR SALTS

(57) Abstract:

PURPOSE: To provide the subject novel compound having an excellent inhibiting effect against HIV infection, low in toxicity, high in safety, and useful as a virus infection-inhibiting agent for human acquired immunodeficiency syndromes.

CONSTITUTION: A glycyrrhetic acid-related compound of formula I [R1 is 1-18C alkyl; R2 is a group produced by combining one-seven SO₃M groups (M is H, alkali metal, alkaline earth metal atom) with the hydroxyl groups of a hydroxyl group-removed lactose residue]. For example, methyl-3-O-[2,3,4,6-tetra(sodium- sulfonato)-β-D-galactopyranosyl (1→4)-2,3,6-tri(sodiumsulfonato)-β-D-glucopyranosyl]glyrrhetinate. The compound of formula I is obtained e.g. by reacting glycyrrhetic acid of formula II as a starting raw material with a specific alcohol, a saccharide compound and furthermore an inorganic or organic base, and subsequently combining the all hydroxyl groups of the produced compound of formula III [R4 is the residue of a disaccharide (lactose)] with SO₃M groups at an adjusted pH.



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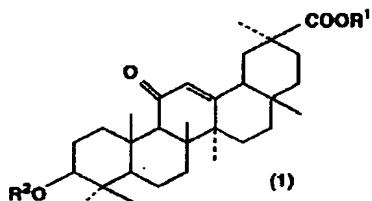
(54)【発明の名称】 新規なグリチルレチン酸関連化合物又はそれらの塩

(57)【要約】

【目的】ヒト後天性免疫不全症候群ウィルス感染阻害剤の有効成分として有用な化合物を提供する。

【構成】一般式(1)

【化1】



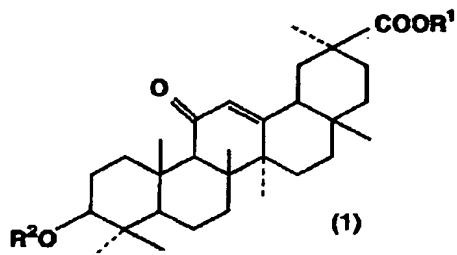
〔式中R¹は炭素数1～18のアルキル基、R²はラクトースから水酸基を除いた残基の水酸基にSO₃M(Mは水素原子又はアルカリ金属、アルカリ土類金属原子)が1～7個結合しているものを示す〕で表わされるグリチルレチン酸関連化合物又はそれらの薬理学的に許容される塩。

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【特許請求の範囲】

【請求項1】一般式(1)

【化1】



〔式中R¹は炭素数1～18のアルキル基、R²はラクトースから水酸基を除いた残基の水酸基にSO₃M（Mは水素原子又はアルカリ金属、アルカリ土類金属原子）が1～7個結合しているものを示す〕で表されるグリチルレチン酸関連化合物又はそれらの薬理学的に許容される塩。

【請求項2】請求項1に示すグリチルレチン酸関連化合物又はそれらの薬理学的に許容される塩を有効成分とするヒト後天性免疫不全症候群ウィルス感染阻害剤。

【発明の詳細な説明】

【0001】

【産業上の利用分野】本発明は、グリチルレチン酸関連化合物を有効成分とするヒト後天性免疫不全症候群ウィルス感染阻害剤に関するものである。

【0002】

【従来の技術】後天性免疫不全症候群（以下エイズと言う）はウィルス（以下エイズウィルス（HIV）と言う）による疾患であることが解明され、現在アシドチミジン、ジデオキシシチジン等の抗エイズウィルス剤が用いられている。一方、グリチルリチンは *in vitro* でHIVの増殖を抑制することが示されており、「伊藤正彦ら、医学のあゆみ、141 427（1987）」また更にグリチルリチン硫酸化物はグリチルリチンの4倍強い活性が報告されている。〔Nakashima et al., Jpn, J, Cancer Res., 78 767 (1987).〕

【0003】

【発明が解決しようとする課題】しかし、現在用いられている抗エイズウィルス剤は毒性が高く、新規な安全性の高い薬剤が望まれている。

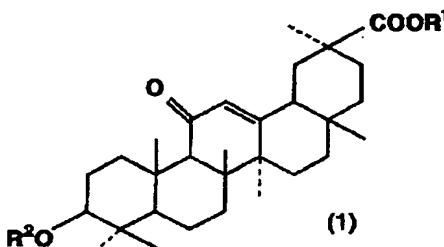
【0004】

【課題を解決するための手段】そこで発明者らは種々検討した結果、新規なグリチルレチン酸関連化合物の硫酸化物及びそれらの塩が従来知られているグリチルリチン及びその硫酸化物ナトリウム塩より数十～百倍強力な抗エイズウィルス作用を有し、抗エイズウィルス剤として使用しうることを見い出した。即ち本発明は一般式(1)

【0005】

【化2】

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【0006】〔式中R¹は炭素数1～18のアルキル基、R²はラクトースから水酸基を除いた残基の水酸基にSO₃M（Mは水素原子又はアルカリ金属、アルカリ土類金属原子）が1～7個結合しているものを示す〕で表されるグリチルレチン酸関連化合物又はそれらの薬理学的に許容される塩に関するものである。

【0007】本発明を更に詳細に説明すると、本発明における一般式(1)においてR¹は炭素数1～18の直鎖のアルキル基を表わし、例えばメチル基、エチル基、プロピル基、ブチル基、ベンチル基、ヘキシル基、ヘプチル基、オクチル基、ノニル基、デシル基、ウンデシル基、ドデシル基、テトラデシル基、ヘキサデシル基、オクタデシル基等を示す。R²として好ましくはメチル基、エチル基、プロピル基、ブチル基、ベンチル基、ヘキシル基、ヘプチル基、オクチル基、ノニル基、デシル基、ウンデシル基、ドデシル基等が挙げられる。

【0008】R²としてはラクトースから水酸基を除いた残基の水酸基にSO₃M（Mは水素原子、あるいはリチウム、ナトリウム、カリウム等のアルカリ金属原子、あるいはマグネシウム、カルシウム等のアルカリ土類金属原子）が1～7個結合しているもので光学活性のあるものは光学異性体も含むものである。

【0009】R²として具体的には2, 3, 4, 6-テトラ(ソジウム スルホナト)-β-D-ガラクトビラノシリル(1→4)-2, 3, 6-トリ(ソジウム スルホナト)-β-D-グルコビラノシリル基に硫酸基の結合した二糖類のナトリウム塩等である。

【0010】一般式(1)の置換基R¹、R²として好ましいものは以上に挙げたものであるが、特に好ましい一般式(1)の化合物としては

(1) メチル 3-O-{2, 3, 4, 6-テトラ(ソジウム スルホナト)-β-D-ガラクトビラノシリル(1→4)-2, 3, 6-トリ(ソジウム スルホナト)-β-D-グルコビラノシリル} グリチルレティナート

(2) エチル 3-O-{2, 3, 4, 6-テトラ(ソジウム スルホナト)-β-D-ガラクトビラノシリル(1→4)-2, 3, 6-トリ(ソジウム スルホナト)-β-D-グルコビラノシリル} グリチルレティナート

(3) プロピル 3-O-{2, 3, 4, 6-テトラ(ソジウム スルホナト)-β-D-ガラクトビラノシリル(1→4)-2, 3, 6-トリ(ソジウム スルホナト)-β-D-グルコビラノシリル} グリチルレティナート

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ル (1→4) -2, 3, 6-トリ (ソジウム スルホナト) - β -D-グルコビラノシル} グリチルレティナート

(4) ブチル 3-O- {2, 3, 4, 6-テトラ (ソジウム スルホナト) - β -D-ガラクトビラノシル (1→4) -2, 3, 6-トリ (ソジウム スルホナト) - β -D-グルコビラノシル} グリチルレティナート

【0011】 (5) ベンチル 3-O- {2, 3, 4, 6-テトラ (ソジウム スルホナト) - β -D-ガラクトビラノシル (1→4) -2, 3, 6-トリ (ソジウム スルホナト) - β -D-グルコビラノシル} グリチルレティナート

(6) ヘキシル 3-O- {2, 3, 4, 6-テトラ (ソジウム スルホナト) - β -D-ガラクトビラノシル (1→4) -2, 3, 6-トリ (ソジウム スルホナト) - β -D-グルコビラノシル} グリチルレティナート

(7) ヘプチル 3-O- {2, 3, 4, 6-テトラ (ソジウム スルホナト) - β -D-ガラクトビラノシル (1→4) -2, 3, 6-トリ (ソジウム スルホナト) - β -D-グルコビラノシル} グリチルレティナート

(8) オクチル 3-O- {2, 3, 4, 6-テトラ (ソジウム スルホナト) - β -D-ガラクトビラノシル (1→4) -2, 3, 6-トリ (ソジウム スルホナト) - β -D-グルコビラノシル} グリチルレティナート

【0012】 (9) ノニル 3-O- {2, 3, 4, 6-テトラ (ソジウム スルホナト) - β -D-ガラク

トビラノシル (1→4) -2, 3, 6-トリ (ソジウム スルホナト) - β -D-グルコビラノシル} グリチルレティナート

(10) デシル 3-O- {2, 3, 4, 6-テトラ (ソジウム スルホナト) - β -D-ガラクトビラノシル (1→4) -2, 3, 6-トリ (ソジウム スルホナト) - β -D-グルコビラノシル} グリチルレティナート

(11) ウンデシル 3-O- {2, 3, 4, 6-テトラ (ソジウム スルホナト) - β -D-ガラクトビラノシル (1→4) -2, 3, 6-トリ (ソジウム スルホナト) - β -D-グルコビラノシル} グリチルレティナート

(12) ドデシル 3-O- {2, 3, 4, 6-テトラ (ソジウム スルホナト) - β -D-ガラクトビラノシル (1→4) -2, 3, 6-トリ (ソジウム スルホナト) - β -D-グルコビラノシル} グリチルレティナート

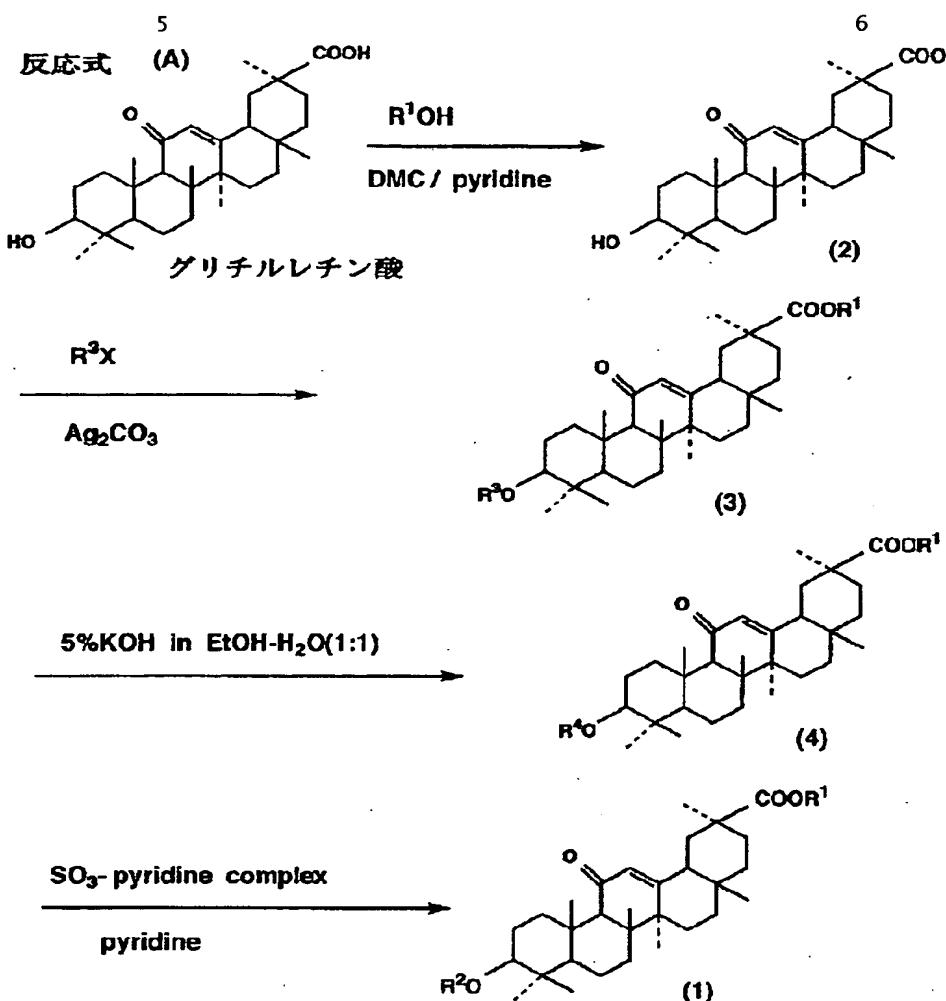
(13) オクタデシル 3-O- {2, 3, 4, 6-テトラ (ソジウム スルホナト) - β -D-ガラクトビラノシル (1→4) -2, 3, 6-トリ (ソジウム スルホナト) - β -D-グルコビラノシル} グリチルレティナート

である。

【0013】 本発明の一般式 (1) で表わされる誘導体は以下の様な反応式 (A) により製造することができる。

【0014】

【化3】



【0015】即ち、乾燥ビリジン等の溶剤に溶解しDM C (2-クロロ-1, 3-ジメチルイミダゾリニウムクロライド)等を用い、あるいは4-ジメチルアミノビリジン存在下又は非存在下にクロロホルム、ジクロロメタン等の溶剤中、N, N'-ジシクロヘキシルカルボジイミド等を用い、あるいはクロロホルム、ジクロロメタン等の溶剤中、1-エチル-3-(3'-ジメチルアミノプロビル)カルボジイミドハイドロクロライドとトリエチルアミン等の塩基を用い、あるいは塩基存在下カルボニルジイミダゾール等を用いてグリチルレチン酸と一般式R¹OHで表わされるアルコールを反応させ一般式(2)で表わされる化合物を得る。次に一般式(2)で表わされる化合物を乾燥ジクロロメタン等の溶剤に溶解し、ドライライトおよび炭酸銀存在下一般式R³X [R³Xはラクトース誘導体等が縮合した(二糖類)ものの1位の水酸基がフッ素、塩素、シュウ素等のハロゲン原子(X)で置換され、その他の水酸基は全てアセチル基等の保護基で保護されている化合物を示す]で表わされる糖化合物を反応させ、式(3)の化合物を得る。

【0016】式(3)の化合物は更に、水、メタノール、エタノール、プロパノール等のアルコール系溶剤中、あるいはそれらの混合溶剤中、水酸化ナトリウム、

水酸化カリウム、炭酸ナトリウム、炭酸カリウム、炭酸水素ナトリウム、炭酸水素カリウム等の無機塩基、あるいはアンモニア水、メチルアミン、エチルアミン、ジメチルアミン、ジエチルアミン、トリメチルアミン、トリエチルアミン等の有機塩基で反応させR³の保護基を脱保護し式(4)の化合物を得る。R³は二糖類(ラクトース)の残基である。次に式(4)の化合物を乾燥ビリジン等の溶媒に溶解し、遮光下又は非遮光下に無水硫酸-ビリジン錯体、あるいはクロロスルホン酸等を反応させ、更にLiOH、NaOH、KOH等の水酸化アルカリ金属、あるいはMg(OH)₂、Ca(OH)₂等の水酸化アルカリ土類金属化合物等の溶液で反応液のpHを調整することによって糖の全ての水酸基にSO₃⁻ (M (Mは水素原子、又はアルカリ金属、アルカリ土類金属原子)が結合した式(1)の化合物を得る。

【0017】上記のグリチルレチン酸から式(1)の化合物までの製造において、溶剤としては上記に記載された溶剤に限らずヘキサン、ベンゼン、トルエン、四塩化炭素、クロロホルム、ジクロロメタン、ジエチルエーテル、ジイソプロピルエーテル、酢酸エチル、酢酸メチル、テトラヒドロフラン、ジオキサン、メタノール、エタノール、プロパノール、イソプロパノール、ジメチル

スルホキシド、N, N-ジメチルホルムアミド、N, N-ジメチルアセトアミド、水、およびそれらの混合溶剤でも反応を行うことができる。

【0018】温度は特に制限はなく氷冷下から溶剤の沸点付近で、好ましくは室温で1~2日間必要に応じて遮光下に反応を行う。反応後の処理としては、通常の手法に従い、必要に応じて沈澱物をろ別、あるいは反応液又はろ液を氷水中に注ぎ、反応液を酢酸エチル、ジエチルエーテル、テトラヒドロフラン、ジクロロメタン、クロロホルム、トルエン、ベンゼン、キシレン等の溶剤に溶解し、希塩酸、希硫酸、希硝酸等の酸、又は希水酸化ナトリウム水溶液、希炭酸ナトリウム水溶液、希炭酸水素カリウム水溶液、希アンモニア水等の塩基あるいは水で洗浄する。洗浄後、無水硫酸マグネシウム、無水硫酸ナトリウム等の乾燥剤で乾燥、乾燥剤をろ別後、ろ液を必要に応じて減圧下で又は常圧下で濃縮する。

【0019】精製法としては得られた濃縮残渣をシリカゲル、アルミナ、けいそう土等、あるいはそれらを各種コーティング剤で修飾した充填剤を用い、常圧から数百気圧の圧力下、順層又は逆層のカラムクロマトグラフィーにかけ、ヘキサン、トルエン、エーテル、酢酸エチル、酢酸メチル、ジクロロメタン、クロロホルム、アセトン、テトラヒドロフラン、ジオキサン、エタノール、メタノール、水、酢酸、ジメチルスルホキシド、N, N-ジメチルホルムアミド、トリエチルアミン、アンモニア水等又はそれらの適当な比率の混合溶媒で溶出する方法、又は同様の溶媒又はそれらの適当な比率の混合溶媒を用いて再結晶又は再沈澱あるいはそれらの方法を組み合わせて行なう。

【0020】本化合物が抗エイズウィルス剤として用いられる場合は、単独または賦形剤あるいは担体と混合して注射剤、経口剤、または坐剤などとして投与される。賦形剤及び担体としては薬剤学的に許容されるものが選ばれ、その種類及び組成は投与経路や投与方法によって決まる。例えば液状担体として水、アルコール類もしくは大豆油、ピーナツ油、ゴマ油、ミネラル油等の動植物油または合成油が用いられ、固体担体として乳糖、マルトース、シクロロースなどの糖類、アミノ酸類、ヒドロキシプロビルセルロースなどセルロース誘導体、ステアリン酸マグネシウムなどの有機酸塩などが使用される。

【0021】注射剤で使用する賦形剤はマンニトール、マルトース、デキストラン、乳糖、シクロデキストリン、コンドロイチン硫酸、ゼラチン、ヒト血清アルブミンであるが、マルトース、乳糖、コンドロイチン硫酸、ゼラチン、ヒト血清アルブミンが好ましい。これらの賦*

表1: IFA法によるエイズウィルス(HIV)に対する活性

化合物番号 ($\mu\text{g}/\text{ml}$)	HIV抗原陽性細胞 (%)			EC ₅₀ ($\mu\text{g}/\text{ml}$)	
	(細胞毒性: - ~ + + +)				
グリチルリチン	1	10	100	1000	
	>90	>90	>90	<1	500

*形剤と共に凍結乾燥剤とし、それを投与時に注射用の適当な溶剤、例えば滅菌水、生理食塩水、ブドウ糖液、電解質溶液アミノ酸液等静脈投与用液体に溶解して投与することもできる。また、本発明における製剤の組成中にpH調整等の目的で、酸やアルカリ又は適量の緩衝剤を加えてもよい。

【0022】製剤中における本化合物の含量は製剤により種々異なるが通常0.1~100重量%、好ましくは1~98重量%である。例えば注射液の場合には、通常10 0.1~30重量%、好ましくは1~10重量%の有効成分を含むようになることがよい。経口投与する場合には、前記固体担体もしくは液状担体とともに錠剤、カプセル剤、粉剤、顆粒剤、液剤、ドライシロップ剤等の形態で、用いられる。カプセル、錠剤、顆粒、粉剤は一般に5~100重量%、好ましくは25~98重量%の有効成分を含む。投与量は、患者の年齢、体重、症状、治療目的等により決定されるが治療量は一般に、非経口投与で1~100mg/kg・日、経口投与で5~500mg/kg・日である。本化合物は比較的低毒性であり、また、連続投与による毒性の蓄積性が小さいことが特徴である。

【0023】

【作用】本発明化合物がHIVの感染を阻害する効果について試験例で示す。

試験例 本発明化合物のHIVに対する活性

試験方法 (IFA法)

抗HIV活性評価は、星野ら(注)の方法に従いおこなった。48穴プレートにまいたMT-4細胞(0.5×10³ cells/0.5ml)に、50μlの各種濃度の被験化合物を添加して2時間インキュベートした後、50μlのHIV(5×10⁴~1×10⁵ PFU/ml)を感染させた。4日後、各穴について一部の細胞を集め、スライドグラス上にアセトンで固定してから、間接蛍光抗体法(1次抗体としてAIDS患者の血清を、2次抗体としてフルオレセインイソチオシアネート(FITC)標識抗ヒトIgGを用いた)により、HIV抗原陽性となった細胞の割合を判定した。(注. THE JOURNAL OF ANTI BIOTICS Vol. 40, No. 7, pp 1077-1078 July 1988, ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Vol. 33, No. 5, May 1989, p 773-775)結果を表1に示す。

【0024】

【表1】

表1: IFA法によるエイズウィルス(HIV)に対する活性

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(6)

10

	(-)	(-)	(-)	(-)	
グリチルリチン	>90	>90	80	<1	440
硫酸化物ナトリウム塩	(-)	(-)	(-)	(-)	
化合物(1)	>90	10	<1	×	5.5
	(-)	(-)	(-)	(++)	
化合物(6)	80	5	<1	×	4.6
	(-)	(-)	(-)	(++)	
化合物(11)	>90	25	<1	×	6.5
	(-)	(-)	(-)	(++)	
化合物(13)	>90	80	<1	×	44
	(-)	(-)	(-)	(++)	

コントロール: 90%、 ×: 判定不能

グリチルリチン硫酸化物ナトリウム塩: 3-O- {2, 3, 4-トリ(ソジウムスルホナト) β -D-グルクロノピラノシリル (1→2) - 3, 4-ジ(ソジウムスルホナト) - β -D-グルクロノピラノシリル} グリチルリチン

【0025】

【実施例】次に本発明を実施例により具体的に説明する。

(1) エステル化反応 (グリチルレチン酸→式(2)の化合物)

実施例1 ウンデシル グリチルレティナート(14)

(式(2): R^1 = ウンデシル) の合成

グリチルレチン酸(5g)をdry pyridineに溶かし、n-ウンデシルアルコール(5ml)、DMC(3.6g)を加え、室温で24時間攪拌した。反応液をCH₂Cl₂で抽出後、5% HCl、飽和重曹水溶液および水で順次洗浄し、乾燥後、減圧濃縮で得た残渣をカラムクロマトグラフィー(benzene-acetone, gradient up to 4.0%)に付し、化合物(14)(4.8g, yield 83.7%)を得た。

【0026】 EI-MS m/z (rel. intensity): 624 (M⁺), 607(19), 606(34), 592(15), 563(17), 458(29), 457(72), 417(18), 416(35), 217(20), 216(14), 192(10), 189(37), 175(44), 174(12), 173(18), 161(15), 159(12), 149(20), 148(11), 147(17), 145(10), 136(13), 135(100).

¹H-NMR(CDCl₃) δ : 0.81, 0.81, 1.01, 1.13, 1.14, 1.15, 1.37(each 3H, s, CH₃)

0.88 (3H, t, J=7.0Hz, -CH₂CH₃)

1.26 (18H, s, -CH₂- × 9)

2.34 (1H, s, H-9),

2.79 (1H, broad d, J=13.6Hz, H-18)

3.23 (1H, dd, J=10.3 and 5.9Hz, H-3)

4.09 (2H, t, J=7.0Hz, -COOCH₂-)

5.65 (1H, s, H-12).

Anal. Calcd for C₁₆H₂₂O₄: C, 78.79; H, 10.97.

Found: C, 78.83; H, 10.77.

DMC: 2-クロロ-1, 3-ジメチルイミダゾリニウム

20 30 35 40 50

後、抽出液を合わせ、5% HCl、飽和重曹水溶液および水で順次洗浄し、硫酸マグネシウム上で乾燥後、減圧濃縮で得た残渣をカラムクロマトグラフィー(benzene-acetone, gradient up to 4.0%)に付し、化合物(15)(14.8g, yield 83.7%)を得た。

【0028】 EI-MS m/z (rel. intensity): 554 (M⁺), 537(15), 536(34), 521(21), 493(23), 388(16), 387(46), 346(34), 217(21), 216(14), 201(11), 189(35), 187(11), 175(39), 174(14), 173(20), 161(18), 159(14), 149(20), 148(13), 147(20), 145(11), 136(12), 135(100).

¹H-NMR(CDCl₃) δ : 0.81, 0.81, 1.01, 1.13, 1.14, 1.15, 1.37(each 3H, s, CH₃)
0.89 (3H, t, J=6.6Hz, -CH₂CH₃)
1.33 (8H, s, -CH₂- × 4)
2.34 (1H, s, H-9),
2.79 (1H, broad d, J=13.6Hz, H-18)
3.22 (1H, dd, J=10.3 and 5.9Hz, H-3)
4.09 (2H, t, J=6.6Hz, -COOCH₂-)
5.65 (1H, s, H-12).

Anal. Calcd for C₁₆H₂₂O₄: C, 77.93; H, 10.54.

Found: C, 71.81; H, 10.35.

【0029】 実施例3 オクタデシル グリチルレティナート(16) (式(2)、 R^1 = オクタデシル) の合成

グリチルレチン酸(50g)をdry pyridineに溶かし、1-オクタデカノール(60g)、DMC(36g)を加え、室温で24時間攪拌した。反応液をCH₂Cl₂(150ml × 3)で抽出後、抽出液を合わせ、5% HCl、飽和重曹水溶液および水で順次洗浄し、硫酸マグネシウム上で乾燥後、減圧濃縮で得た残渣をカラムクロマトグラフィー(benzene-acetone, gra

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dient up to 2.0%) に付し、化合物 (16) (57.9g, yield 74.4%)を得た。

【0030】FAB-MS(m/z) 745 [M+Na]⁺

¹H-NMR($CDCl_3$) δ : 0.81, 0.81, 1.01, 1.13, 1.14, 1.15, 1.37(each 3H, s, CH_3)
0.88 (3H, t, J =6.6Hz, $-CH_2CH_3$)
1.25 (32H, s, $-CH_2-$ \times 16)
2.34 (1H, s, H-9),
2.80 (1H, broad d, J =13.6Hz, H-18)
3.23 (1H, dd, J =9.9 and 5.9Hz, H-3)
4.09 (2H, t, J =7.0Hz, $-COOCH_2-$)
5.65 (1H, s, H-12).

Anal. Calcd for $C_{18}H_{22}O_4$: C, 79.72 ; H, 11.43.

Found : C, 79.58 ; H, 11.49.

【0031】(2) グリコシル化反応 (式(2)の化合物→式(3)の化合物)

実施例4. 化合物 (18)、(式(3)) ; R^1 = ウンデシル、 R^3 = ヘプタ- O -アセチル-ラクトシル) の合成

化合物 (14) (1.8g) を dry CH_2Cl_2 に溶かし容器を遮光して、Drierite(1g)および Ag_2CO_3 (3g)を加え 1 時間攪拌後、ヘプタ- O -アセチル-ラクトシル-プロマイド (6.5g) を加えて、さらに室温で 2 日間攪拌した。反応液をろ過後、ろ液を冰水 (100ml) 中に注ぎ込み、 CH_2Cl_2 (80ml \times 3) で抽出、抽出液を合わせ、飽和重曹水、水で順次洗浄し、硫酸マグネシウム上で乾燥した。ろ過後、ろ液を濃縮して得た残渣をカラムクロマトグラフィー (benzene-EtOAc, gradient up to 4%) および高速液体クロマトグラフィー-HPLC[ODS 10mm \times 250mm(MeOH)]を行い精製後、化合物 (18) (1.8g, yield 50.3%)を得た。

【0032】FAB-MS(m/z) 1265 [M+Na]⁺

Anal. Calcd for $C_6H_{10}O_2$: C, 64.71 ; H, 8.27.

Found : C, 64.36 ; H, 8.40.

¹H-NMR($CDCl_3$)

アグリコン

Me 1.35, 1.14, 1.12, 1.11, 0.92, 0.80, 0.76(each s)

$COOCH_3$ 4.08 (t, J =6.2Hz)

(CH_3) 1.26 (s, 18H)

CH_2CH_3 0.88 (t, J =6.2Hz)

H-3 3.08 (t, J =8.4Hz)

H-9 2.31 (s)

H-12 5.65 (s)

H-18 2.79 (broad d, J =13.6Hz)

インナーシュガー

H-1 4.47 (d, J =8.1Hz)

H-2 4.94 (dd, J =9.2, 8.1Hz)

H-3 5.19 (t, J =9.2Hz)

H-4 3.72 (t, J =9.2Hz)

H-5 3.60 (ddd, J =9.2, 6.2, 1.8Hz)

12

H-6 4.41 (dd, J =11.7, 1.8Hz)

H-6' 4.06-4.16 (overlapped)

アウターシュガー

H-1 4.50 (d, J =7.7Hz)

H-2 5.11 (dd, J =10.3, 7.7Hz)

H-3 4.95 (dd, J =10.3, 2.6Hz)

H-4 5.34 (d, J =2.6Hz)

H-5 3.88 (t, J =6.6Hz)

H-6 4.04 ~4.16 (overlapped)

10 H-6' 4.04 ~4.16 (overlapped)

Ac 2.15, 2.09, 2.06, 2.05, 2.04, 2.02, 1.96 (each s)

【0033】実施例5 化合物 (20) (式(3)) ; R^1 = メチル、 R^3 = ヘプタ- O -アセチル-ラクトシル) の合成

メチル グリチルレティナート (19) (2.0g) を dry CH_2Cl_2 に溶かし容器を遮光して、Drierite(1g)および Ag_2CO_3 (4.5g)を加え 1 時間攪拌後、ヘプタ- O -アセチル-ラクトシル-プロマイド (11.0g)を加えて、さらに室温で 2 日間攪拌した。反応液をろ過後、ろ液を冰水 (100ml) 中に注ぎ込み、 CH_2Cl_2 (80ml \times 3) で抽出、抽出液を合わせ、飽和重曹水、水で順次洗浄し、硫酸マグネシウム上で乾燥した。ろ過後、ろ液を濃縮して得た残渣をカラムクロマトグラフィー (benzene-EtOAc, gradient up to 4%) および高速液体クロマトグラフィー-HPLC[ODS 10mm \times 250mm(MeOH)]を行い精製後、化合物 (20) (2.6g, yield 57.0%)を得た。

【0034】mp. 214-215 °C

FAB-MS(m/z) 1125 [M+Na]⁺

30 ¹H-NMR($CDCl_3$)

アグリコン

Me 1.36, 1.14, 1.12, 1.11, 0.93, 0.81, 0.76(each s)

$COOCH_3$ 3.96 (s)

H-3 3.09 (t, J =7.9Hz)

H-9 2.31 (s)

H-12 5.65 (s)

H-18 2.78 (broad d, J =11.4Hz)

インナーシュガー

40 H-1 4.52 (d, J =8.1Hz)

H-2 4.93 (dd, J =9.5, 8.1Hz)

H-3 5.19 (t, J =9.5Hz)

H-4 3.74 (t, J =9.5Hz)

H-5 3.65 (ddd, J =9.5, 6.6, 1.8Hz)

H-6 4.42 (dd, J =11.0, 1.8Hz)

H-6' 4.05-4.16 (overlapped)

アウターシュガー

H-1 4.52 (d, J =8.1Hz)

H-2 5.10 (dd, J =10.3, 8.1Hz)

50 H-3 4.97 (dd, J =10.3, 3.3Hz)

H-4	5.34 (t, $J=3.3\text{Hz}$)
H-5	3.92 (t, $J=6.6\text{Hz}$)
H-6	4.05 ~4.16 (overlapped)
H-6'	4.05 ~4.16 (overlapped)
Ac	2.15, 2.18, 2.06, 2.05, 2.04, 2.02, 1.98 (each s)

Anal. Calcd for $C_{11}H_{16}O_2$: C, 62.05; H, 7.49.

Found: C, 62.23; H, 7.43.

【0035】実施例6. 化合物(21) (式(3)) ; R^1 = ヘキシル、 R^3 = ヘプタ- O -アセチル-ラクトシルの合成

化合物(15)(2.0g)をdry CH_2Cl_2 に溶かし容器を遮光して、Drierite(1g)および Ag_2CO_3 (3.5g)を加え1時間攪拌後、ヘプタ- O -アセチル-ラクトシル-プロマイド(9.0g)を加えて、さらに室温で2日間攪拌した。反応液をろ過後、ろ液を冰水(100ml)中に注ぎ込み、 CH_2Cl_2 (80ml × 3)で抽出。抽出液を合わせ、飽和重曹水、水で順次洗浄し、硫酸マグネシウム上で乾燥した。ろ過後、ろ液を濃縮して得た残渣をカラムクロマトグラフィー(benzene-EtOAc, gradient up to 8%)および高速液体クロマトグラフィー-HPLC [ODS 10mm × 250mm(MeOH)]を行い精製後、化合物(21)(2.3g, yield 52.0%)を得た。

【0036】FAB-MS(m/z) 1195 [M+Na]⁺

Anal. Calcd for $C_{11}H_{16}O_2$: C, 63.46; H, 7.90.

Found: C, 63.29; H, 8.21.

¹H-NMR(CDCl_3)

アグリコン

Me 1.35, 1.33, 1.14, 1.12, 0.92, 0.80, 0.75(each s)

COOCH₂ 4.04 ~4.16 (overlapped)

(CH₂) 1.32 (s, 8H)

CH₂CH₃ 0.89 (t, $J=6.6\text{Hz}$)

H-3 3.08 (t, $J=8.1\text{Hz}$)

H-9 2.31 (s)

H-12 5.64 (s)

H-18 2.79 (broad d, $J=13.6\text{Hz}$)

インナーシュガー

H-1 4.48 (d, $J=7.7\text{Hz}$)

H-2 4.93 (dd, $J=9.5, 7.7\text{Hz}$)

H-3 5.19 (t, $J=9.5\text{Hz}$)

H-4 3.72 (t, $J=9.5\text{Hz}$)

H-5 3.61 (ddd, $J=9.5, 5.9, 1.8\text{Hz}$)

H-6 4.42 (dd, $J=11.7, 1.8\text{Hz}$)

H-6' 4.04 ~4.16 (overlapped)

アウターシュガー

H-1 4.51 (d, $J=8.1\text{Hz}$)

H-2 5.11 (dd, $J=10.6, 8.1\text{Hz}$)

H-3 4.95 (dd, $J=10.6, 3.3\text{Hz}$)

H-4 5.35 (t, $J=3.3\text{Hz}$)

H-5 3.88 (t, $J=6.6\text{Hz}$)

H-6 4.04 ~4.16 (overlapped)

H-6' 4.04 ~4.16 (overlapped)

Ac 2.15, 2.09, 2.06, 2.05, 2.04, 2.02, 1.96
(each s)

【0037】実施例7. 化合物(22) (式(3)) ; R^1 = オクタデシル、 R^3 = ヘプタ- O -アセチル-ラクトシルの合成

化合物(16)(2.0g)をdry CH_2Cl_2 に溶かし容器を遮光して、Drierite(1g)および Ag_2CO_3 (3.5g)を加え1時間攪拌後、ヘプタ- O -アセチル-ラクトシル-プロマイド(7.3g)を加えて、さらに室温で2日間攪拌した。反応液をろ過後、ろ液を冰水(100ml)中に注ぎ込み、 CH_2Cl_2 (80ml × 3)で抽出。抽出液を合わせ、飽和重曹水、水で順次洗浄し、硫酸マグネシウム上で乾燥した。ろ過後、ろ液を濃縮して得た残渣をカラムクロマトグラフィー(benzene-EtOAc, gradient up to 4%)および高速液体クロマトグラフィー-HPLC [ODS 10mm × 250mm(MeOH)]を行い精製後、化合物(22)(1.5g, yield 40.4%)を得た。

【0038】FAB-MS(m/z) 1363 [M+Na]⁺

Anal. Calcd for $C_{17}H_{34}O_2$: C, 66.24; H, 8.71.

Found: C, 66.36; H, 8.65.

¹H-NMR(CDCl_3)

アグリコン

Me 1.35, 1.14, 1.12, 1.12, 0.92, 0.80, 0.76(each s)

COOCH₂ 4.08 (t, $J=6.2\text{Hz}$)

(CH₂) 1.25 (s, 32H)

CH₂CH₃ 0.88 (t, $J=6.2\text{Hz}$)

H-3 3.08 (t, $J=8.1\text{Hz}$)

30 H-9 2.31 (s)

H-12 5.64 (s)

H-18 2.79 (broad d, $J=13.2\text{Hz}$)

インナーシュガー

H-1 4.48 (d, $J=7.7\text{Hz}$)

H-2 4.93 (dd, $J=9.5, 7.7\text{Hz}$)

H-3 5.19 (t, $J=9.5\text{Hz}$)

H-4 3.72 (t, $J=9.5\text{Hz}$)

H-5 3.60 (ddd, $J=9.5, 6.2, 1.8\text{Hz}$)

H-6 4.41 (dd, $J=11.7, 1.8\text{Hz}$)

40 H-6' 4.04 ~4.16 (overlapped)

アウターシュガー

H-1 4.50 (d, $J=7.3\text{Hz}$)

H-2 5.10 (dd, $J=10.3, 7.3\text{Hz}$)

H-3 4.95 (dd, $J=10.3, 2.9\text{Hz}$)

H-4 5.34 (t, $J=2.9\text{Hz}$)

H-5 3.88 (t, $J=6.3\text{Hz}$)

H-6 4.04 ~4.16 (overlapped)

H-6' 4.04 ~4.16 (overlapped)

Ac 2.15, 2.09, 2.06, 2.05, 2.04, 2.02, 1.96
(each s)

【0039】(3) 脱保護基反応 (式(3)の化合物→式(4)の化合物)

実施例8. 化合物(23)；ウルデシル 3-O- { β -D-ガラクトビラノシリル (1→4) - β -D-グルコビラノシリル} グリチルレティナートの合成

化合物(18)(1.5g)を5% KOH in EtOH-H₂O (1:1)(25ml)に溶かし、1晩静置した後、酢酸で中和し、減圧濃縮して得た残渣をカラムクロマトグラフィー (CHCl₃:MeOH:H₂O=65:35:20 ~ 10 lower phase) で精製後化合物(23)(8.20mg, yield 70.9%)を得た。

〔 α 〕²⁵ +58.4(c=1.0, pyridine)

FAB-MS m/z : 971 [M+Na]⁺

Anal. Calcd for C₅₃H₆₈O₁₄ · 1/2 H₂O : C, 66.29 ; H, 9.54.

Found C, 66.38 ; H, 9.36

【0040】¹³C-NMR(C₅D₅N) δ :

アグリコンC-1 39.5

2 26.4

3 88.7

4 39.8

5 55.4

6 17.6

7 32.9

8 44.2

9 61.9

10 37.3

11 199.3

12 128.7

13 169.0

14 45.5

15 26.6

16 26.5

17 32.1

18 48.7

19 41.3

20 43.4

21 31.4

22 38.2

23 28.2

24 16.7

25 17.0

26 18.8

27 23.5

28 28.7

29 29.1

30 176.4

-OCH₂- 64.6

-CH₂- 14.3

-CH₂- 32.1

29.8 × 2

29.7

29.5

29.4

28.3

26.7

22.9

インナーシュガー

C-1 105.7

2 75.2

10 3 77.1

4 82.5

5 76.8

6 62.5

アウターシュガー

C-1 106.4

2 75.1

3 72.5

4 69.9

5 76.1

20 6 62.1

スペクトルは重ビリジン (C₅D₅N) 中で測定。

【0041】実施例9. 化合物(24)；メチル 3-O- { β -D-ガラクトビラノシリル (1→4) - β -D-グルコビラノシリル} グリチルレティナートの合成

化合物(20)(1.8g)を5% KOH in EtOH-H₂O (1:1)(35ml)に溶かし、1晩静置した後、酢酸で中和し、減圧濃縮して得た残渣をカラムクロマトグラフィー (CHCl₃:MeOH:H₂O=65:35:20 ~ 10 lower phase) で精製後化合物(24)(1.1mg, yield 82.7g)を得た。

30 〔 α 〕²⁵ +87.3(c=1.0, pyridine)

FAB-MS m/z : 831 [M+Na]⁺

Anal. Calcd for C₄₃H₆₈O₁₄ · 1/2 H₂O : C, 63.14 ; H, 8.50.

Found C, 63.24 ; H, 8.38

【0042】¹³C-NMR(C₅D₅N) δ :

アグリコンC-1 42.5

2 29.6

3 91.8

4 42.9

40 5 54.8

6 20.7

7 35.9

8 47.2

9 65.0

10 40.3

11 202.6

12 131.7

13 172.2

14 48.6

50 15 29.8

16	26.5	7	32.9
17	35.1	8	44.2
18	51.7	9	61.9
19	44.3	10	37.2
20	46.4	11	199.4
21	34.3	12	128.6
22	41.2	13	169.2
23	31.2	14	45.5
24	19.8	15	26.7
25	20.1	16	25.9
26	21.8	17	32.0
27	24.5	18	48.7
28	31.2	19	41.3
29	31.6	20	43.4
30	179.9	21	31.3
-OCH ₃	68.4	22	28.1
インナーシュガー		23	28.3
C-1	108.8	24	16.7
2	78.3	25	17.0
3	80.1	26	18.8
4	85.5	27	23.4
5	79.9	28	28.1
6	65.5	29	28.7
アウターシュガー		30	176.4
C-1	109.5	-OCH ₃ -	64.5
2	78.2	-CH ₃	14.1
3	75.5	-CH ₂ -	31.5
4	73.0		29.0
5	79.2		22.7 × 2
6	65.1	30	インナーシュガー

【0043】実施例10. 化合物(25)；ヘキシル 3-O- { β -D-ガラクトピラノシリル (1→4) - β -D-グルコピラノシリル} グリチルレティナートの合成
化合物(21)(1.6g)を5% KOH in EtOH-H₂O (1:1)(30ml)に溶かし、1晩静置した後、酢酸で中和し、減圧濃縮して得た残渣をカラムクロマトグラフィー (CHCl₃ : MeOH : H₂O=65:35:20 ~ 10 lower phase) で精製後化合物(25)(1.0g, yield 82.5%)を得た。

$[\alpha]^{20} + 81.9$ (c=1.0, pyridine)

FAB-MS m/z : 901 [M+Na]⁺

Anal. Calcd for C₄₃H₇₀O₁₄ · 1/2 H₂O : C, 64.91 ; H, 8.97.

Found C, 64.94 ; H, 8.86

【0044】¹³C-NMR(C, D, N)δ :

アグリコンC-1 39.4

2 26.5

3 88.7

4 39.8

5 55.3

6 17.6

C-1	105.7
2	75.1
3	77.1
4	82.3
5	76.8
6	62.3
30	インナーシュガー
C-1	106.4
2	75.1
3	72.4
4	69.9
5	76.1
6	62.1

【0045】実施例11 化合物(26)；オクタデシル 3-O- { β -D-ガラクトピラノシリル (1→4) - β -D-グルコピラノシリル} グリチルレティナートの合成
化合物(22)(1.2g)を5% KOH in EtOH-H₂O (1:1)(25ml)に溶かし、1晩静置した後、酢酸で中和し、減圧濃縮して得た残渣をカラムクロマトグラフィー (CHCl₃ : MeOH : H₂O=65:35:20 ~ 10 lower phase) で精製後化合物(26)(7

65mg, yield 81.0% を得た。
 $[\alpha]^{20} = +55.3$ (c=1.0, pyridine)

mp. 246 ~ 247 °C

FAB-MS m/z : 1069 [M + Na]⁺

Anal. Calcd for C₆H₁₀O₄ · 1/2 H₂O : C, 68.21 ;

H, 9.84.

Found C, 67.87 ; H, 9.62.

【0046】¹³C-NMR(C₆D₆N) δ :

アグリコンC-1 39.3

2 26.5

3 88.7

4 39.7

5 55.3

6 17.5

7 32.8

8 44.0

9 61.7

10 37.1

11 199.2

12 128.6

13 168.8

14 45.4

15 26.6

16 26.2

17 32.0

18 48.5

19 41.2

20 43.3

21 31.2

22 38.0

23 28.3

24 16.6

25 16.8

26 18.7

27 23.4

28 28.6

29 28.9

30 176.1

-OCH₂- 64.4

-CH₃ 14.2

-CH₂- 31.9

29.8 × 4

29.7 × 3

29.6

29.5

29.3

28.9

26.3

22.8

インナーシュガー

C-1 105.4

2 74.7

3 76.7

4 82.1

5 76.4

6 76.2

アウトアーシュガー

C-1 106.1

2 74.7

10 3 72.0

4 69.7

5 75.7

6 61.9

【0047】(4) 硫酸化反応 (式(4)の化合物→式(1)の化合物)

実施例12. 化合物(11) : ウンデシル 3-O- {2, 3, 4, 6-テトラ(ソジウム スルホナト)- β -D-ガラクトビラノシリル (1→4) -2, 3, 6-トリ(ソジウム スルホナト)- β -D-グルコビラノシリル} グリチルレティナートの合成

化合物(23)(500mg)をdry pyridine(8ml)に溶かし、容器を遮光して、SO₃-Pyridine Complex(1.8g)を加え室温で24時間攪拌した。反応液のpHを1M NaOHでpH 8~9に調整し、H₂O-MeOH(1:1)(30ml)で希釈し、減圧濃縮して残渣を得た。この残渣の水溶液(5ml)をDiaion HP-20に付し、吸着させた後水洗し、50% MeOH(150ml)で溶出し、化合物(11)(673mg yield 75.9%)を得た。

【 α 】²⁰ = +32.4° (c=1.0, H₂O)

FAB-MS m/z : 1685 [M + Na]⁺

30 【0048】¹³C-NMR(D₂O) (内部標準物質 ジオキサン) δ :

アグリコンC-1 41.1

2 29.4

3 93.1

4 41.7

5 56.5

6 18.8

7 35.1

8 46.6

40 9 56.9

10 39.1

11 204.9

12 130.4

13 173.6

14 48.0

15 29.4

16 28.7

17 34.2

18 50.5

50 19 43.0

20	45.8	4	39.9
21	33.5	5	55.4
22	40.9	6	18.0
23	31.1	7	33.3
24	17.6	8	44.9
25	18.3	9	58.3
26	21.3	10	37.3
27	25.3	11	203.5
28	30.1	12	128.5
29	31.9	13	172.7
30	180.2	14	46.3
-OCH ₂ -	67.1	15	27.2
-CH ₃	16.5	16	26.3
-CH ₂ -	34.4 × 2	17	32.5
32.3 × 3		18	49.1
31.3		19	41.4
25.1 × 2		20	44.1
21.6		21	31.5
インナーシュガー		22	38.9
C-1	102.9	23	27.8
2	75.8	24	16.6
3	80.1	25	17.0
4	82.1	26	19.6
5	77.9	27	23.6
6	64.0	28	28.4
アウターシュガー		29	29.5
C-1	105.5	30	179.8
2	74.5	-OCH ₃	53.2
3	69.7	インナーシュガー	
4	68.2	30	C-1 101.2
5	77.7	2	74.1
6	64.0	3	78.3
【0049】実施例13. 化合物(1)；メチル 3-O- - {2, 3, 4, 6-テトラ(ソジウム スルホナト) -β-D-ガラクトビラノシリル(1→4)-2, 3, 6 -トリ(ソジウム スルホナト)-β-D-グルコビラ ノシリル} グリチルレティナートの合成		4	80.5
化合物(24)(500mg)をdry pyridine(8ml)に溶かし、容器を遮光して、SO ₃ -Pyridine Complex(2.1g)を加え室温で24時間攪拌した。反応液のpHを1M NaOHでpH 8~9に調整し、H ₂ O-MeOH(1:1)(30ml)で希釈し、減圧濃縮して残渣を得た。この残渣の水溶液(5ml)をDiaion HP-20に付し、吸着させた後水洗し、50% MeOH(150ml)で溶出し、化合物(1)(806mg yield 84.6%)を得た。		5	76.2
【0050】[α] ²⁰ + 57.3 (c=1.0, H ₂ O) FAB-MS m/z: 1545 [M + Na] ⁺ ¹³ C-NMR(D ₂ O)：(内部標準物質 ジオキサン) アグリコンC-1 39.6		6	62.4
2 27.2		アウターシュガー	
3 91.5		C-1 103.8	
		2 72.9	
		3 68.1	
		40 4 66.7	
		5 76.0	
		6 62.4	
		【0051】実施例14. 化合物(6)；ヘキシリル 3-O- - {2, 3, 4, 6-テトラ(ソジウム スルホナ ト)-β-D-ガラクトビラノシリル(1→4)-2, 3-6-トリ(ソジウム スルホナト)-β-D-グル コビラノシリル} グリチルレティナートの合成	
		化合物(25)(500mg)をdry pyridine(8ml)に溶かし、容器を遮光して、SO ₃ -Pyridine Complex(1.9g)を加え室温で24時間攪拌した。反応液のpHを1M NaOHでpH 8~9に	

調整し、H₂O-MeOH(1:1)(30ml) で希釈し、減圧濃縮して残渣を得た。この残渣の水溶液(5ml) をDiaion HP-20に付し、吸着させた後水洗し、50% MeOH(150ml) で溶出し、化合物(6) (672mg, yield 73.3%)を得た。

【0052】 $[\alpha]^{20} + 46.0$ (c=1.0, H₂O)

FAB-MS m/z: 1615 [M + Na]⁺

¹³C-NMR(D₂O): (内部標準物質 ジオキサン) δ:

アグリコンC-1 39.6

2 27.2

3 91.5

4 39.9

5 55.3

6 17.7

7 33.3

8 44.8

9 58.2

10 37.4

11 202.9

12 128.7

13 171.7

14 46.3

15 27.2

16 26.4

17 32.5

18 48.9

19 41.4

20 44.1

21 31.7

22 39.1

23 28.4

24 16.6

25 17.0

26 19.6

27 23.5

28 27.7

29 29.3

30 178.2

-OCH₂- 65.5

-CH₃ 14.7

-CH₂- 32.0

29.6

23.2 ×2

インナーシュガー

C-1 101.3

2 74.1

3 78.3

4 80.5

5 76.3

6 62.4

アウターシュガー

C-1 103.7

2 72.9

3 68.0

4 66.7

5 76.0

6 62.4

【0053】 実施例15. 化合物(13); オクタデシル

3-O- {2, 3, 4, 6-テトラ(ソジウム スルホ

ナト) -β-Dガラクトピラノシリル(1→4) -2,

10 3, 6-トリ(ソジウム スルホナト) -β-D-グル

コピラノシリル} グリチルレティナートの合成

化合物(26)(500mg)をdry pyridine(8ml) に溶かし、容器を遮光して、SO₂-Pyridine Complex(1.3g)を加え室温で24時間攪拌した。反応液のpHを1M NaOH でpH 8~9に調整し、H₂O-MeOH(1:1)(30ml) で希釈し、減圧濃縮して残渣を得た。この残渣の水溶液(5ml) をDiaion HP-20に通し、吸着させた後水洗し、50% MeOH(150ml) で溶出し、化合物(13) (683mg, yield 80.4%)を得た。

【0054】 $[\alpha]^{20} + 35.8$ (c=1.0, H₂O)

20 ¹³C-NMR(D₂O): (内部標準物質 ジオキサン) δ:

アグリコンC-1 39.5

2 27.3

3 91.4

4 40.0

5 55.1

6 18.1

7 33.3

8 44.9

9 58.3

30 10 37.4

11 202.9

12 128.8

13 171.4

14 46.2

15 27.3

16 27.0

17 32.5

18 48.8

19 41.2

40 20 44.1

21 31.7

22 39.2

23 28.5

24 16.7

25 17.1

26 19.6

27 23.6

28 27.7

29 29.5

50 30 178.2

-OCH ₃ -	65.3
-CH ₃	14.7
-CH ₂ -	23.4 × 2
29.6	
30.2 × 2	
30.5 × 5	
30.6 × 4	
32.7 × 2	
インナーシュガー	
C - 1	101.3
2	74.1
3	78.5
4	80.4
5	76.3
6	62.3
アウターシュガー	
C - 1	103.7
2	72.9
3	68.0
4	66.6
5	76.3
6	62.2

【0055】実施例16

注射剤

化合物番号6、10重量部、乳糖20重量部、1N-塩酸及び注射用蒸留水(適量)によりpH4.0に調整し

た薬液500重量部を得る。この調整した薬液をメンブランフィルターで除菌ろ過した後、注射用ガラス容器に分注し、凍結乾燥する。凍結乾燥終了後、1バイアルに化合物番号6(100mg)を含む凍結乾燥注射用製剤を得る。

【0056】実施例17

顆粒剤

化合物番号6 50重量部、乳糖600部、結晶セルロース330部及びヒドロキシプロピルセルロース20部10をよく混和し、ロール型圧縮機(ローラーコンパクター登録商標)を用いて圧縮し、破碎して16メッシュと60メッシュの間にに入るよう篩過し、顆粒とした。

【0058】実施例18

錠剤

化合物番号6 30重量部、結晶乳糖120部、結晶セルロース147部及びステアリン酸マグネシウム3部をV型混合機で混合後、打錠し、1錠300mgの錠剤を得た。

【0058】

20 【発明の効果】本発明のグリチルレチン酸関連化合物はHIVの感染に対しグリチルリチン、グリチルリチン硫酸化物ナトリウム塩の数十から数百倍の優れた阻止効果を示し、毒性も低く安全性も高いことにより、ヒト後天性免疫不全症候群ウィルス感染阻害剤の有効成分として有用である。